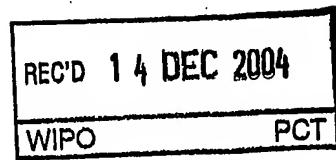


EP04/051455

**Bescheinigung****Certificate****Attestation**

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten internationalen Patentanmeldung überein.

The attached documents are exact copies of the international patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet international spécifiée à la page suivante.

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09. 12. 2004

Der Präsident des Europäischen Patentamts  
Im Auftrag  
For the President of the European Patent Office  
Le Président de l'Office européen des brevets  
p. o.

S. Spreafico

Patentanmeldung Nr.  
Patent application no.  
Demande de brevet n°

PCT/EP 03/50310

Blatt 2 der Bescheinigung  
Sheet 2 of the certificate  
Page 2 de l'attestation

Anmeldung Nr.:  
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Demande n°:

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## PCT REQUEST

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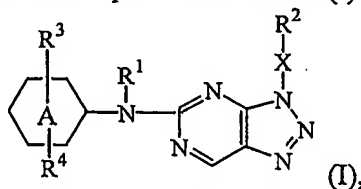
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V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	US

# TRIAZOLOPYRIMIDINE DERIVATIVES AS GLYCOGEN SYNTHASE KINASE 3 INHIBITORS

The present invention concerns a novel group of compounds, their use as a medicine,  
5 their use for the manufacture of a medicament for the treatment of diseases mediated  
through glycogen synthase kinase 3 (GSK3), in particular glycogen synthase kinase 3 $\alpha$   
and 3 $\beta$ ; processes for their preparation and pharmaceutical compositions comprising  
them.

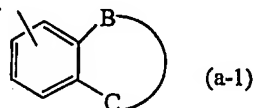
- 10 WO 00/62778 describes cyclic protein tyrosine kinase inhibitors. In particular, it  
discloses thiazolyl derivatives comprising a bicyclic ring system.  
WO 01/44246 describes bicyclic pyrimidine and pyridine based compounds having  
GSK3 inhibiting activity.  
WO 99/65897 describes pyrimidine and pyridine based compounds having GSK3  
15 inhibiting activity.  
WO 02/04450 describes purine derivatives having the activity of either inhibiting the  
formation of amyloid beta or stimulating the formation of sbeta-amyloid precursor  
protein.
- 20 The present invention relates to compounds, which are distinguishable from the prior  
art in structure, pharmacological activity, potency and/or selectivity.

The present invention concerns a compound of formula (I)



- 25 a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a  
stereochemically isomeric form thereof, wherein  
ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;  
 $R^1$  represents hydrogen; aryl; formyl;  $C_{1-6}$ alkylcarbonyl;  $C_{1-6}$ alkyl;  
 $C_{1-6}$ alkyloxycarbonyl;  $C_{1-6}$ alkyl substituted with formyl,  $C_{1-6}$ alkylcarbonyl,  
30  $C_{1-6}$ alkyloxycarbonyl,  $C_{1-6}$ alkylcarbonyloxy; or  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylcarbonyl  
optionally substituted with  $C_{1-6}$ alkyloxycarbonyl;  
X represents a direct bond;  $C_{1-4}$ alkyl- or  $-C_{1-2}$ alkyl- $X_a-X_b-$ ;  
with  $X_a$  representing O or  $NR^5$ ; and

with  $X_b$  representing a direct bond or  $C_{1-2}$ alkyl;  
 $R^2$  represents  $C_{3-7}$ cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical of formula



wherein  $-B-C-$  represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$  (b-1);

$-CH_2-CH_2-CH_2-CH_2-$  (b-2);

$-X_1-CH_2-CH_2-(CH_2)_n-$  (b-3);

$-X_1-CH_2-(CH_2)_n-X_1-$  (b-4);

$-X_1-(CH_2)_n-CH=CH-$  (b-5);

with  $X_1$  representing O or  $NR^5$ ;

$n$  representing an integer with value 0, 1, 2 or 3;

$n'$  representing an integer with value 0 or 1;


wherein said  $R^2$  substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy;  $C_{1-6}$ alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ;  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ; polyhalo $C_{1-6}$ alkyl;  $C_{1-6}$ alkyloxy optionally substituted with carboxyl; polyhalo $C_{1-6}$ alkyloxy;  $C_{1-6}$ alkylthio; polyhalo $C_{1-6}$ alkylthio;  $C_{1-6}$ alkyloxycarbonyl;  $C_{1-6}$ alkylcarbonyloxy;  $C_{1-6}$ alkylcarbonyl; polyhalo $C_{1-6}$ alkylcarbonyl; cyano; carboxyl;  $NR^6R^7$ ;  $C(=O)NR^6R^7$ ;  $-NR^5-C(=O)-NR^6R^7$ ;  $-NR^5-C(=O)-R^5$ ;  $-S(=O)_{n1}-R^8$ ;  $-NR^5-S(=O)_{n1}-R^8$ ;  $-S-CN$ ;  $-NR^5-CN$ ; aryloxy; arylthio; arylcarbonyl; aryl $C_{1-4}$ alkyl; aryl $C_{1-4}$ alkyloxy; a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N and said 5- or 6-membered monocyclic heterocycle optionally being substituted with at least one substituent selected from  $R^9$ ; or

$-(CH_2)_{n2}-X_2-(CH_2)_{n2}-N \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} X_3 \\ X_3 \end{array}$ ;

with  $n_2$  representing an integer with value 0, 1, 2, 3 or 4;

with  $X_2$  representing O,  $NR^5$  or a direct bond;

with  $X_3$  representing O or  $NR^5$ ;

- $R^3$  represents halo; hydroxy;  $C_{1-6}$ alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ;  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ; polyhalo $C_{1-6}$ alkyl;  $C_{1-6}$ alkyloxy optionally substituted with carboxyl; polyhalo $C_{1-6}$ alkyloxy;  $C_{1-6}$ alkylthio; polyhalo $C_{1-6}$ alkylthio;  $C_{1-6}$ alkyloxycarbonyl;  $C_{1-6}$ alkylcarbonyloxy;  $C_{1-6}$ alkylcarbonyl; polyhalo $C_{1-6}$ alkylcarbonyl; nitro; cyano; carboxyl;  $NR^6R^7$ ;  $C(=O)NR^6R^7$ ;  $-NR^5-C(=O)-NR^6R^7$ ;  $-NR^5-C(=O)-R^5$ ;  $-S(=O)_{n1}-R^8$ ;  $-NR^5-S(=O)_{n1}-R^8$ ;  $-S-CN$ ;  $-NR^5-CN$ ;
- $R^4$  represents hydrogen; halo; hydroxy;  $C_{1-4}$ alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^{10}R^{11}$ ,  $-C(=O)-NR^{10}R^{11}$ ,  $-NR^5-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_{n1}-R^{12}$  or  $-NR^5-S(=O)_{n1}-R^{12}$ ;  $C_{2-4}$ alkenyl or  $C_{2-4}$ alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^{10}R^{11}$ ,  $-C(=O)-NR^{10}R^{11}$ ,  $-NR^5-C(=O)-NR^{10}R^{11}$ ,  $-S(=O)_{n1}-R^{12}$  or  $-NR^5-S(=O)_{n1}-R^{12}$ ; polyhalo $C_{1-3}$ alkyl;  $C_{1-4}$ alkyloxy optionally substituted with carboxyl; polyhalo $C_{1-3}$ alkyloxy;  $C_{1-4}$ alkylthio; polyhalo $C_{1-3}$ alkylthio;  $C_{1-4}$ alkyloxycarbonyl;  $C_{1-4}$ alkylcarbonyloxy;  $C_{1-4}$ alkylcarbonyl; polyhalo $C_{1-4}$ alkylcarbonyl; nitro; cyano; carboxyl;  $NR^{10}R^{11}$ ;  $C(=O)NR^{10}R^{11}$ ;  $-NR^5-C(=O)-NR^{10}R^{11}$ ;  $-NR^5-C(=O)-R^5$ ;  $-S(=O)_{n1}-R^{12}$ ;  $-NR^5-S(=O)_{n1}-R^{12}$ ;  $-S-CN$ ;  $-NR^5-CN$ ;
- $R^5$  represents hydrogen or  $C_{1-4}$ alkyl;
- $R^6$  and  $R^7$  each independently represent hydrogen; cyano;  $C_{1-6}$ alkylcarbonyl;  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl;  $C_{1-4}$ alkyl- $NR^5-C_{1-4}$ alkyl;  $C_{1-6}$ alkyl optionally substituted with hydroxy,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyloxy,  $NR^{6a}R^{7a}$ ,  $C(=O)NR^{6a}R^{7a}$ ,
- ; with  $X_4$  representing O or  $NR^5$ ;
- $R^{6a}$  and  $R^{7a}$  each independently represent hydrogen;  $C_{1-4}$ alkyl;  $C_{1-4}$ alkylcarbonyl; a 5- or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N;
- $R^8$  represents  $C_{1-4}$ alkyl, polyhalo $C_{1-4}$ alkyl or  $NR^6R^7$ ;

- $R^9$  represents halo; hydroxy;  $C_{1-6}$ alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ;  $C_{2-6}$ alkenyl or  $C_{2-6}$ alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,  $C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,  $-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ; polyhalo $C_{1-6}$ alkyl;  $C_{1-6}$ alkyloxy optionally substituted with carboxyl; polyhalo $C_{1-6}$ alkyloxy;  $C_{1-6}$ alkylthio; polyhalo $C_{1-6}$ alkylthio;
- $C_{1-6}$ alkyloxycarbonyl;  $C_{1-6}$ alkylcarbonyloxy;  $C_{1-6}$ alkylcarbonyl; cyano; carboxyl;  $NR^6R^7$ ;  $C(=O)NR^6R^7$ ;  $-NR^5-C(=O)-NR^6R^7$ ;  $-NR^5-C(=O)-R^5$ ;  $-S(=O)_{n1}-R^8$ ;  $-NR^5-S(=O)_{n1}-R^8$ ;  $-S-CN$ ;  $-NR^5-CN$ ;
- $R^{10}$  and  $R^{11}$  each independently represent hydrogen;  $C_{1-6}$ alkyl; cyano;  $C_{1-6}$ alkylcarbonyl;  $C_{1-4}$ alkyloxy $C_{1-4}$ alkyl or  $C_{1-4}$ alkyl- $NR^5-C_{1-4}$ alkyl;
- $R^{12}$  represents  $C_{1-4}$ alkyl or  $NR^{10}R^{11}$ ;
- $n1$  represents an integer with value 1 or 2;
- aryl represents phenyl or phenyl substituted with at least one substituent selected from halo,  $C_{1-6}$ alkyl,  $C_{3-7}$ cycloalkyl,  $C_{1-6}$ alkyloxy, cyano, nitro, polyhalo $C_{1-6}$ alkyl and polyhalo $C_{1-6}$ alkyloxy.
- The present invention also relates to the use of a compound of formula (I) for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.
- As used herein  $C_{1-2}$ alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 2 carbon atoms such as methyl, ethyl;  $C_{1-3}$ alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 3 carbon atoms such as the groups defined for  $C_{1-2}$ alkyl and propyl, 1-methylethyl;  $C_{1-4}$ alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as the groups defined for  $C_{1-3}$ alkyl and butyl;  $C_{1-6}$ alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the groups defined for  $C_{1-4}$ alkyl and pentyl, hexyl, 2-methylbutyl and the like;  $C_{2-4}$ alkenyl as a group or part of a group defines straight and branched chain hydrocarbon radicals having from 2 to 4 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl and the like;  $C_{2-6}$ alkenyl as a group or part of a group defines straight and branched chain hydrocarbon radicals having from 2

to 6 carbon atoms containing a double bond such as the groups defined for C<sub>2-4</sub>alkenyl and pentenyl, hexenyl and the like; C<sub>2-4</sub>alkynyl as a group or part of a group defines straight and branched chain hydrocarbon radicals having from 2 to 4 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl and the like; C<sub>2-6</sub>alkynyl as  
5 a group or part of a group defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as the group defined for C<sub>2-4</sub>alkynyl and pentynyl, hexynyl and the like; C<sub>3-7</sub>cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N  
10 comprises saturated, partially saturated or aromatic 4, 5, 6- or 7-membered monocyclic heterocycles containing at least one heteroatom selected from O, N or S; saturated heterocycles are heterocycles containing only single bonds; partially saturated heterocycles are heterocycles containing at least one double bond provided that the ring system is not an aromatic ring system; the term aromatic is well known to a person  
15 skilled in the art and designates cyclically conjugated systems of  $4n' + 2$  electrons, that is with 6, 10, 14 etc.  $\pi$ -electrons (rule of Hückel;  $n'$  being 1, 2, 3 etc.).

Particular examples of 4, 5, 6- or 7-membered saturated monocyclic heterocycles are azetidiny, oxetanyl, tetrahydrofuranyl, pyrrolidinyl, dioxolanyl, imidazolidinyl,  
20 thiazolidinyl, tetrahydrothienyl, dihydrooxazolyl, isothiazolidinyl, isoxazolidinyl, oxadiazolidinyl, triazolidinyl, thiadiazolidinyl, pyrazolidinyl, piperidinyl, hexahydropyrimidinyl, hexahydropyridazinyl, dioxanyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl, homopiperidinyl (azepanyl), [1,3]diazepanyl, homopiperazinyl ([1,4]diazepanyl), [1,2]diazepanyl, oxepanyl, dioxepanyl.

25 Particular examples of 5- or 6-membered partially saturated heterocycles are pyrrolinyl, imidazolinyl, pyrazolinyl and the like.

Particular examples of 4, 5, 6- or 7-membered aromatic monocyclic heterocycles are  
30 pyrrolyl, furyl, thienyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, thiadiazolyl, oxadiazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a  
35 carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.



The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhaloC<sub>1-6</sub>alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C<sub>1-6</sub>alkyl, for example, methyl substituted with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl, 1,1-difluoro-ethyl and the like.

- 5 In case more than one halogen atoms are attached to an alkyl group within the definition of polyhaloC<sub>1-6</sub>alkyl, they may be the same or different.

The term heterocycle as in the definition of for instance R<sup>2</sup> is meant to include all the possible isomeric forms of the heterocycles, for instance, pyrrolyl also includes  
10 2H-pyrrolyl.

- The hereinabove-mentioned heterocycles may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the 5- or 6-membered heterocycle is  
15 imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

When any variable (eg. R<sup>6</sup>, R<sup>7</sup> etc.) occurs more than one time in any constituent, each definition is independent.

- 20 Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms.

- For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are  
25 non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

- 30 The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid;  
35 phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic,

ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

- 5 The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g.
- 10 primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine,
- 15 *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.

- The term addition salt also comprises the hydrates and solvent addition forms which the
- 20 compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

- The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic
- 25 nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyl iodide or benzyl iodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen.
- 30 Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

- The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized to the so-called
- 35 *N*-oxide.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds

5 denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably less than 5%, in particular less than 2% and most preferably less than 1% of the other

10 isomers. In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of

15 this invention.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several tertiary nitrogen atoms are oxidized to the so-called *N*-oxide.

20

Some of the compounds of formula (I) may also exist in their tautomeric form (e.g. keto-enol tautomerism). Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

25 Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their salts, their quaternary amines and their stereochemically isomeric forms. Of special interest are those compounds of formula (I) which are stereochemically pure.

30 Interesting compounds are those compounds of formula (I) as defined hereinabove, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, wherein

ring A represents phenyl or pyridyl;

R<sup>1</sup> represents hydrogen;

35 X represents a direct bond or C<sub>1-4</sub>alkyl;

R<sup>2</sup> represents phenyl wherein said phenyl may optionally be substituted with at least one substituent selected from halo; C<sub>1-6</sub>alkyl optionally substituted with at least one

- substituent selected from hydroxy; C<sub>1-6</sub>alkyloxy; cyano; C(=O)NR<sup>6</sup>R<sup>7</sup>;  
arylC<sub>1-4</sub>alkyloxy; a 5-or 6-membered heterocycle containing at least one heteroatom  
selected from O, S or N and said 5-or 6-membered heterocycle optionally being  
substituted with at least one substituent selected from R<sup>9</sup>;
- 5 R<sup>3</sup> represents halo; hydroxy; C<sub>1-6</sub>alkyl optionally substituted with at least one  
substituent selected from hydroxy, cyano, carboxyl; C<sub>2-6</sub>alkenyl optionally substituted  
with at least one substituent selected from carboxyl, C<sub>1-4</sub>alkyloxycarbonyl;  
polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkyloxycarbonyl; C<sub>1-6</sub>alkylcarbonyl; cyano;  
carboxyl; NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>;  
10 -S-CN;  
R<sup>4</sup> represents hydrogen; halo; C<sub>1-6</sub>alkyl; cyano.

Also interesting compounds are those compounds of formula (I) as defined  
hereinabove, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary  
15 amines and stereochemically isomeric forms thereof, wherein the R<sup>3</sup> substituent is  
linked to ring A in metaposition compared to the NR<sup>1</sup> linker.

Also interesting compounds are those compounds of formula (I) as defined  
hereinabove, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary  
20 amines and stereochemically isomeric forms thereof, wherein the R<sup>4</sup> substituent is  
linked to ring A in paraposition compared to the NR<sup>1</sup> linker.

Interesting compounds are also those compounds of formula (I) as defined hereinabove,  
their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and  
25 stereochemically isomeric forms thereof, wherein the R<sup>2</sup> substituent is unsubstituted or  
substituted with 1, 2 or 3 substituents.

Particular interesting compounds are those compounds of formula (I) as defined  
hereinabove, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary  
30 amines and stereochemically isomeric forms thereof, wherein  
ring A represents phenyl or pyridyl;  
R<sup>1</sup> represents hydrogen;  
X represents a direct bond;  
R<sup>2</sup> represents phenyl wherein said phenyl may optionally be substituted with at least  
35 one substituent selected from halo; C<sub>1-6</sub>alkyloxy; C(=O)NR<sup>6</sup>R<sup>7</sup>; a 5-or 6-membered  
heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-

membered heterocycle optionally being substituted with at least one substituent selected from  $R^9$ ;

$R^3$  represents halo; hydroxy;  $C_{1-6}$ alkyl optionally substituted with at least one substituent selected from hydroxy;  $C_{2-6}$ alkenyl optionally substituted with at least one substituent selected from carboxyl,  $C_{1-4}$ alkyloxycarbonyl; polyhalo $C_{1-6}$ alkyloxy;  $C_{1-6}$ alkyloxy;  $C_{1-6}$ alkylcarbonyl; cyano; carboxyl;  $C(=O)NR^6R^7$ ;  $-S(=O)_{n1}-R^8$ ;  $-NR^5-S(=O)_{n1}-R^8$ ;

$R^4$  represents hydrogen; halo;  $C_{1-6}$ alkyl; cyano.

10 Preferred compounds of formula (I) are compounds 1, 2, 3, 7, 8, 9, 10, 15, 21, 22, 23, 24, 29, 30, 31, 32, 33, 6, 4, 37, 38, 39, 44, 45, as listed in Tables 1 to 3 hereinafter, their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof.

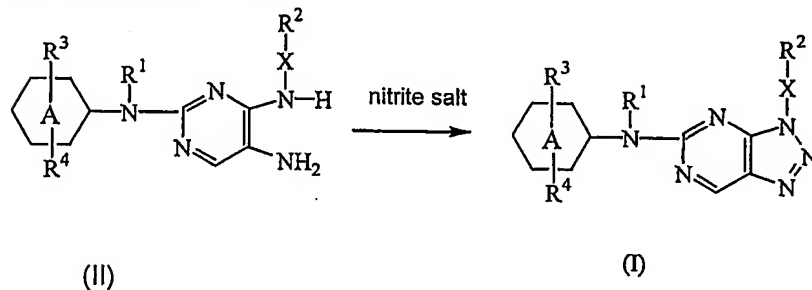
15 Most preferred compounds of formula (I) are selected from :

[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-benzonitrile;  
[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl]-(3-methanesulfonyl-phenyl)-amine;

20 *N*-{3-[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-phenyl}-methanesulfonamide;

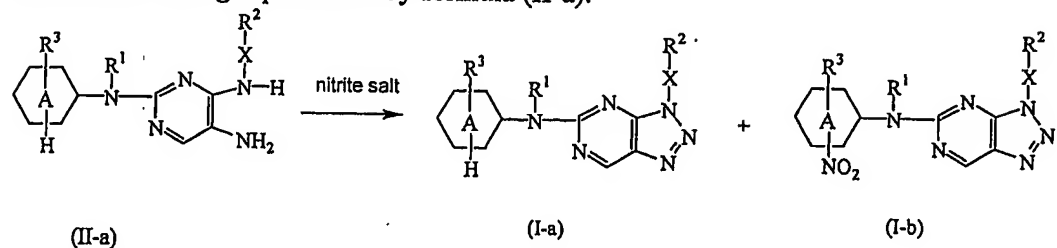
1-{3-[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-phenyl}-ethanone; a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

25 Compounds of formula (I) can be prepared by cyclizing an intermediate of formula (II) in the presence of a nitrite salt, such as for example  $NaNO_2$ , a suitable solvent, such as for example water, and a suitable acid, such as for example hydrochloric acid and/or acetic acid and the like.

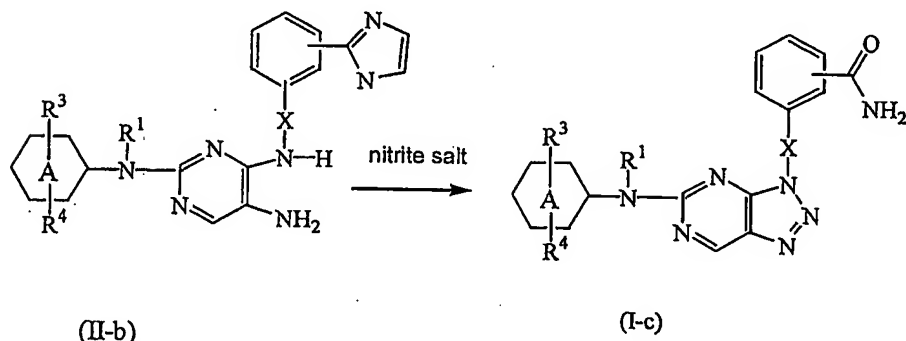


30 The above reaction can also be used to prepare compounds of formula (I) wherein  $R^4$  represents either hydrogen or nitro, said compounds being represented by formula (I-a)

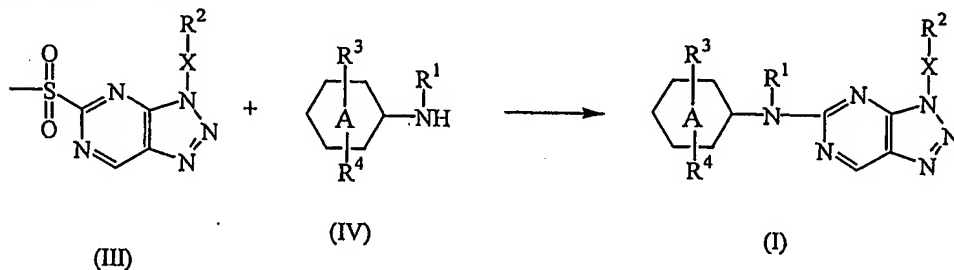
and (I-b), from an intermediate of formula (II) wherein  $R^4$  represents hydrogen, said intermediate being represented by formula (II-a).



5 The above reaction can also be used to prepare a compound of formula (I) wherein  $R^2$  represents a phenyl ring substituted with aminocarbonyl, said compound being represented by formula (I-c), from an intermediate of formula (II) wherein  $R^2$  represents a phenyl ring substituted with an imidazole moiety, said intermediate being represented by formula (II-b).



10 Compounds of formula (I) can also be prepared by reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent, such as for example dimethylsulfoxide,  $\text{CH}_3\text{-O-CH}_2\text{-CH}_2\text{-OH}$  or  $(\text{CH}_3)_2\text{N-C(=O)H}$  in the presence of NaH.



15 In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

5 The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate  
10 organic peroxides may comprise peroxy acids such as, for example, benzenecarboxy-peroxy acid or halo substituted benzenecarboxy-peroxy acid, e.g. 3-chlorobenzenecarboxy-peroxy acid, peroxyalkanoic acids, e.g. peroxyacetic acid, alkylhydroperoxides, e.g. *t*-butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated  
15 hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

Compounds of formula (I) wherein  $R^2$  is a ring system substituted with halo, e.g. bromo, can be converted into a compound of formula (I) wherein said  $R^2$  substituent is unsubstituted, in the presence of  $H_2$  and in the presence of a suitable catalyst, such as  
20 for example palladium on charcoal, a suitable catalyst poison, such as for example a thiophene solution, a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example tetrahydrofuran.

Compounds of formula (I) wherein  $R^3$  is halo, e.g. bromo, can be converted into a compound wherein  $R^3$  is cyano by reaction with Zn and  $Zn(CN)_2$  in the presence of  
25 tris(dibenzylideneacetone)dipalladium, 1,1'-bis(diphenylphosphino)ferrocene and *N,N*-dimethylacetamide.

Compounds of formula (I) wherein  $R^3$  is halo, e.g. bromo, can be converted into a compound wherein  $R^3$  is  $C_{2-6}$ alkenyl optionally substituted with  $C_{1-6}$ alkyloxycarbonyl, by reaction with a  $C_{2-6}$ alkene optionally substituted with  $C_{1-6}$ alkyloxycarbonyl in the  
30 presence 1,3-bis(diphenylphosphino)propane,  $Pd(OAc)_2$ , a suitable base, such as for example *N,N*-diethylethanamine, and a suitable solvent, such as for example tetrahydrofuran.

35 Compounds of formula (I) wherein  $R^3$  is  $C_{2-6}$ alkenyl substituted with  $C_{1-6}$ alkyloxycarbonyl can be converted into a compound of formula (I) wherein  $R^3$  is

C<sub>2-6</sub>alkenyl substituted with carboxyl by reaction with a suitable base, such as sodium hydroxide, in the presence of a suitable solvent, such as for example tetrahydrofuran.

5 Compounds of formula (I) wherein R<sup>3</sup> is -NR<sup>5</sup>-C(=O)-R<sup>5</sup> can be converted into a compound of formula (I) wherein R<sup>3</sup> is NH<sub>2</sub> by reaction with a suitable acid, such as for example HCl, in the presence of a suitable solvent, such as for example an alcohol, e.g. ethanol and the like.

10 Compounds of formula (I) wherein R<sup>2</sup> is substituted with halo can also be converted into a compound of formula (I) wherein R<sup>2</sup> is substituted with C<sub>1-6</sub>alkylthio, by reaction with a reagent of formula alkaline metal<sup>+</sup> S-C<sub>1-6</sub>alkyl, e.g. Na<sup>+</sup> S-C<sub>1-6</sub>alkyl, in the presence of a suitable solvent, such as *N,N*-dimethylsulfoxide. The latter compounds can further be converted into a compound of formula (I) wherein R<sup>2</sup> is substituted with C<sub>1-6</sub>alkyl-S(=O)-, by reaction with a suitable oxidizing agent, such as a peroxide, e.g.  
15 3-chlorobenzenecarboperoxoic acid, in the presence of a suitable solvent, such as an alcohol, e.g. ethanol.

20 Compounds of formula (I) wherein R<sup>3</sup> is halo, or wherein R<sup>2</sup> is substituted with halo can also be converted into a compound of formula (I) wherein R<sup>3</sup> is C<sub>1-6</sub>alkyloxy, or wherein R<sup>2</sup> is substituted with C<sub>1-6</sub>alkyloxy, by reaction with an alcoholate salt, such as, for example, LiOC<sub>1-6</sub>alkyl, in the presence of a suitable solvent, such as an alcohol, e.g. methanol.

25 Compounds of formula (I) wherein R<sup>3</sup> is halo, or wherein R<sup>2</sup> is substituted with halo can also be converted into a compound of formula (I) wherein R<sup>3</sup> is hydroxy, or wherein R<sup>2</sup> is substituted with hydroxy, by reaction with a suitable carboxylate, e.g. sodium acetate, in a suitable reaction-inert solvent, such as, for example, *N,N*-dimethylsulfoxide, followed by treating the obtained reaction product with a suitable base, such as pyridine.

30 Compounds of formula (I) wherein R<sup>3</sup> is chloro, or wherein R<sup>2</sup> is substituted with chloro, can be converted into a compound of formula (I) wherein R<sup>3</sup> is fluoro, or wherein R<sup>2</sup> is substituted with fluoro, by reaction with a suitable fluoride salt, such as for example potassium fluoride, in the presence of a suitable solvent, e.g. sulfolane.

35 Compounds of formula (I) wherein R<sup>2</sup> is substituted with C<sub>1-4</sub>alkyloxyC<sub>1-6</sub>alkyl, can be converted into a compound of formula (I) wherein R<sup>2</sup> is substituted with



hydroxyC<sub>1-6</sub>alkyl, by dealkylating the ether in the presence of a suitable dealkylating agent, such as, for example, tribromoborane, and a suitable solvent, such as methylene chloride.

- 5 Compounds of formula (I) wherein R<sup>3</sup> is C<sub>1-6</sub>alkyloxycarbonyl, or wherein R<sup>2</sup> is substituted with C<sub>1-6</sub>alkyloxycarbonyl, can be converted into a compound of formula (I) wherein R<sup>3</sup> is aminocarbonyl, or wherein R<sup>2</sup> is substituted with aminocarbonyl or mono- or di(C<sub>1-6</sub>alkyl)aminocarbonyl by reaction with a suitable agent such as ammonia, NH<sub>2</sub>(C<sub>1-6</sub>alkyl), AlCH<sub>3</sub>[N(C<sub>1-6</sub>alkyl)<sub>2</sub>]Cl optionally in the presence of a  
10 suitable acid, such as for example hydrochloric acid, and in the presence of a suitable solvent such as an alcohol, e.g. methanol; tetrahydrofuran; *N,N*-diisopropylethane.

- Compounds of formula (I) wherein R<sup>2</sup> is unsubstituted can be converted into a compound wherein R<sup>2</sup> is substituted with halo, by reaction with a suitable halogenating  
15 agent, such as, for example Br<sub>2</sub> or 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis[tetrafluoroborate], in the presence of a suitable solvent, such as tetrahydrofuran, water, acetonitrile, chloroform and optionally in the presence of a suitable base such as *N,N*-diethylethanamine.

- 20 Compounds of formula (I) wherein R<sup>3</sup> is C<sub>1-6</sub>alkyloxycarbonyl or wherein R<sup>2</sup> is substituted with C<sub>1-6</sub>alkyloxycarbonyl, can be converted into a compound of formula (I) wherein R<sup>3</sup> is hydroxymethyl or wherein R<sup>2</sup> is substituted with hydroxymethyl by reaction with a suitable reducing agent, such as for example LiAlH<sub>4</sub>.

- 25 Compounds of formula (I) wherein R<sup>3</sup> is nitro, may be converted into a compound of formula (I) wherein R<sup>3</sup> is amino, by reaction with a suitable reducing agent, such as for example H<sub>2</sub>, in the presence of a suitable catalyst, such as for example palladium on charcoal, a suitable catalyst poison, such as for example a thiophene solution, and a suitable solvent, such as for example an alcohol, e.g. methanol, ethanol and the like.

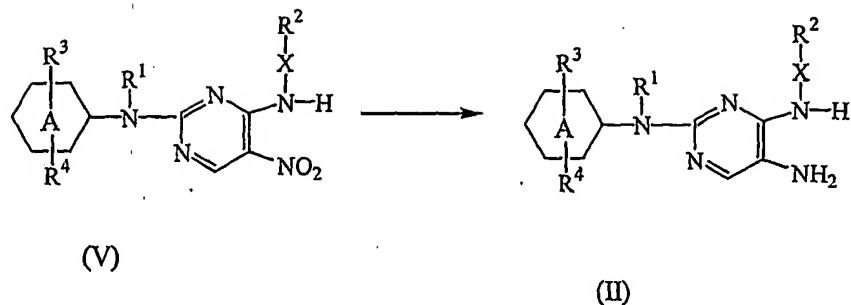
- 30 Compounds of formula (I) wherein R<sup>2</sup> is substituted with NH<sub>2</sub> can be converted into a compound of formula (I) wherein R<sup>2</sup> is substituted with NH-S(=O)<sub>2</sub>-NR<sup>6</sup>R<sup>7</sup> by reaction with W<sub>1</sub>-S(=O)<sub>2</sub>-NR<sup>6</sup>R<sup>7</sup> wherein W<sub>1</sub> represents a suitable leaving group such as for example a halo atom, e.g. chloro, in the presence of a suitable solvent, such as for  
35 example *N,N*-dimethylacetamide and a suitable base, such as for example *N,N*-diethylethanamine.

Some of the compounds of formula (I) and some of the intermediates in the present invention may consist of a mixture of stereochemically isomeric forms. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers  
5 can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically  
10 separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate  
15 intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

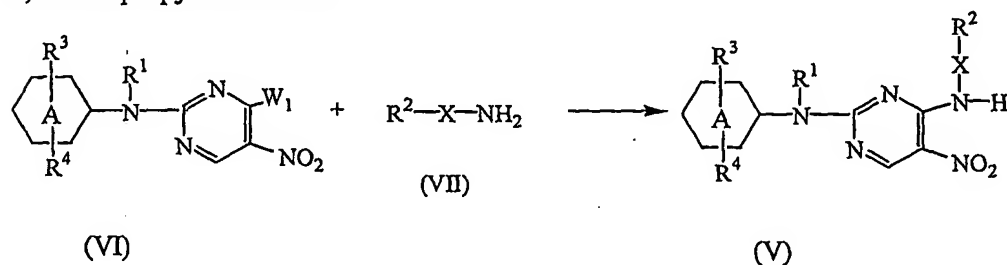
An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid  
20 chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures.

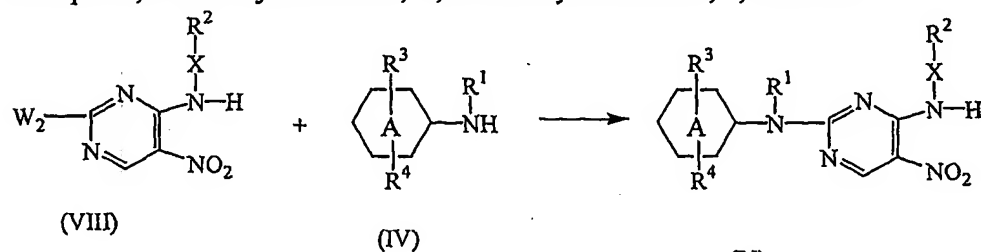
25 Intermediates of formula (II) can be prepared by reducing an intermediate of formula (V) with a suitable reducing agent, such as for example  $H_2$ , in the presence of a suitable catalyst, such as for example platina on charcoal or palladium on charcoal, optionally in the presence of a suitable catalyst poison, such as for example a thiophene solution, optionally in the presence of  $NH_2-NH_2$ , in the presence of a suitable solvent, such as for  
30 example *N,N*-dimethylacetamide, tetrahydrofuran, *N,N*-dimethylformamide or a suitable alcohol, such as for example methanol, ethanol and the like, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



Intermediates of formula (V) can be prepared by reacting an intermediate of formula (VI) wherein  $W_1$  represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, with an intermediate of formula (VII) in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide or an alcohol, e.g. ethanol and the like, and optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.

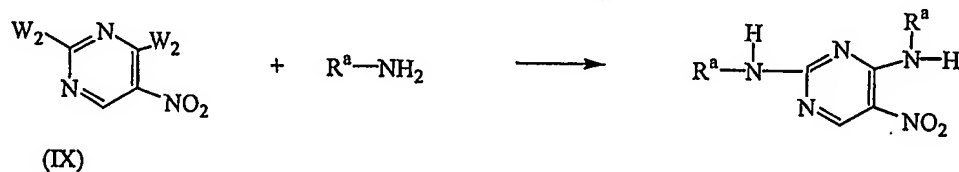


Intermediates of formula (V) can also be prepared by reacting an intermediate of formula (VIII) wherein  $W_2$  represents a suitable leaving group, such as for example halogen, e.g. chloro and the like, with an intermediate of formula (IV) in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine or *N,N*-diethylethanamine, and optionally in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide, 1,4-dioxane.



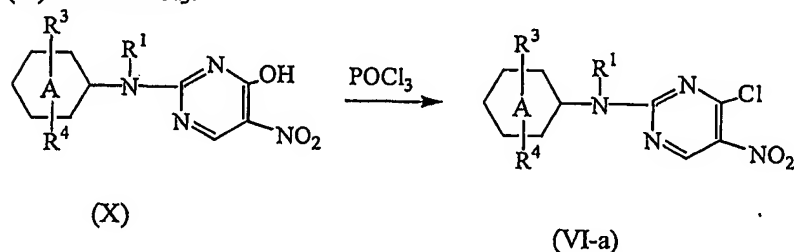
Intermediates of formula (V) wherein  $R^2-X-NH-$  and the moiety represent the same substituent being represented by  $R^a-NH-$ , said intermediates being represented by formula (V-a), can be prepared by reacting an intermediate of formula

(IX) wherein  $W_2$  is defined as herein above, with  $R^a-NH_2$  in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine, and a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide or  $CH_2Cl_2$ .

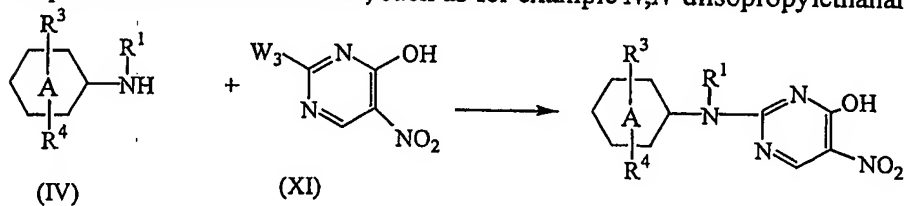


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Intermediates of formula (VI) wherein  $W_1$  represents chloro, said intermediates being represented by formula (VI-a), can be prepared by reacting an intermediate of formula (X) with  $POCl_3$ .



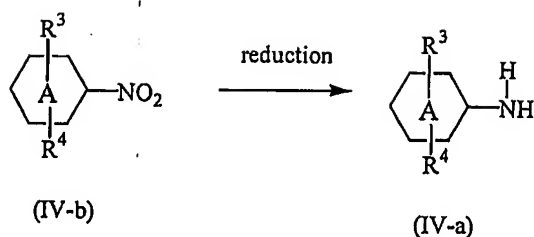
- 10 Intermediates of formula (X) can be prepared by reacting an intermediate of formula (IV) with an intermediate of formula (XI) wherein  $W_3$  represents a suitable leaving group, such as for example halogen, e.g. chloro, in the presence of a suitable solvent, such as for example tetrahydrofuran and water, or  $CH_3-O-(CH_2)_2-OH$ , and optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.



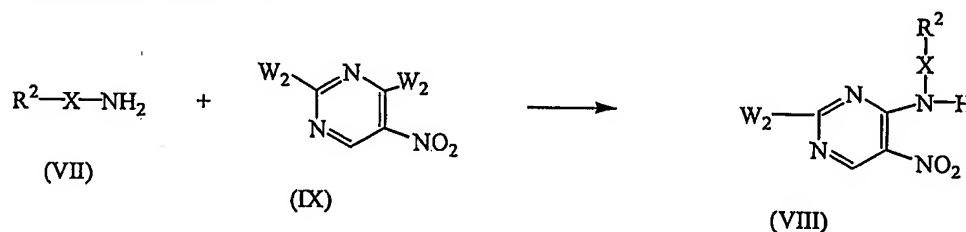
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Intermediates of formula (IV) wherein  $R^1$  represents hydrogen, said intermediates being represented by formula (IV-a), can be prepared by reacting an intermediate of formula (IV-b) with a suitable reducing agent, such as for example  $H_2$ , in the presence of a suitable catalyst, such as for example platina on charcoal or palladium on charcoal, optionally a suitable catalyst poison, such as for example a thiophene solution, a suitable solvent, such as for example *N,N*-dimethylacetamide, tetrahydrofuran, *N,N*-dimethylformamide or a suitable alcohol, such as for example methanol, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.

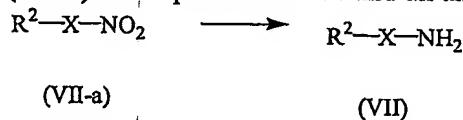
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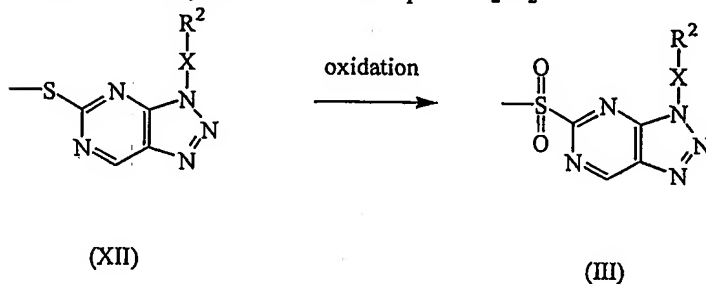
Intermediates of formula (VIII) can be prepared by reacting an intermediate of formula (VII) with an intermediate of formula (IX) in the presence of a suitable solvent, such as for example *N,N*-dimethylacetamide, *N,N*-dimethylformamide,  $\text{CH}_2\text{Cl}_2$  or 1,4-dioxane, and optionally in the presence of a suitable base, such as for example *N,N*-diisopropylethanamine.



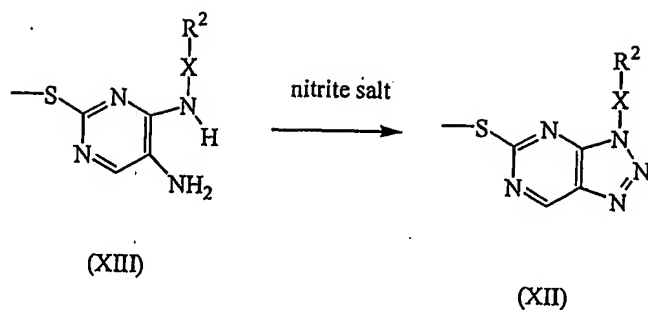
Intermediates of formula (VII) can be prepared by reducing an intermediate of formula (VII-a) in the presence of Fe and an ammonium chloride solution.



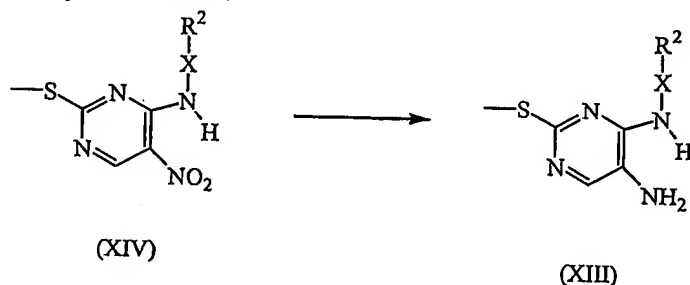
Intermediates of formula (III) can be prepared by reacting an intermediate of formula (XII) with a suitable oxidizing agent, such as for example  $\text{KMnO}_4$ , in the presence of a suitable solvent, such as for example water, and a suitable acid, such as for example acetic acid. An alternative suitable oxidizing agent is meta-chloroperbenzoic acid, in a suitable solvent, such as for example  $\text{CH}_2\text{Cl}_2$ .



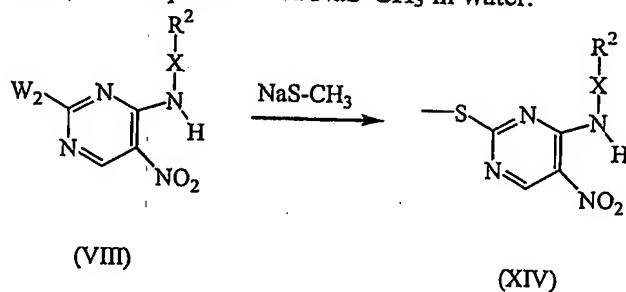
Intermediates of formula (XII) can be prepared by reacting an intermediate of formula (XIII) with a nitrite salt, such as for example  $\text{NaNO}_2$ , a suitable solvent, such as for example water, and a suitable acid, such as for example hydrochloric acid and/or acetic acid and the like.



Intermediates of formula (XIII) can be prepared by reacting an intermediate of formula (XIV) with a suitable reducing agent, such as for example  $H_2$ , in the presence of a suitable catalyst, such as for example platinum on charcoal or palladium on charcoal, optionally a suitable catalyst poison, such as for example a thiophene solution, a suitable solvent, such as for example *N,N*-dimethylacetamide, tetrahydrofuran, *N,N*-dimethylformamide or a suitable alcohol, such as for example methanol, and optionally in the presence of a suitable base, such as for example *N,N*-diethylethanamine.



Intermediates of formula (XIV) can be prepared by reacting an intermediate of formula (VIII), in the presence of  $NaS-CH_3$  in water.



- 15 The compounds of formula (I) inhibit Glycogen synthase kinase 3 (GSK3), in particular glycogen synthase kinase 3 alpha (GSK3 $\alpha$ ) and/or glycogen synthase kinase 3 beta (GSK3 $\beta$ ). They are selective Glycogen synthase kinase 3 inhibitors. Specific inhibitory compounds are superior therapeutic agents since they are characterized by a greater efficacy and lower toxicity by virtue of their specificity.
- 20 Synonyms for GSK3 are tau protein kinase I (TPK I), FA (Factor A) kinase, kinase FA and ATP-citrate lysase kinase (ACLK).

Glycogen synthase kinase 3 (GSK3), which exists in two isoforms as already stated above, i.e. GSK3 $\alpha$  and GSK3 $\beta$ , is a proline-directed serine/threonine kinase originally identified as an enzyme that phosphorylates glycogen synthase. However, it has been  
5 demonstrated that GSK3 phosphorylates numerous proteins in vitro such as glycogen synthase, phosphatase inhibitor I-2, the type-II subunit of cAMP-dependent protein kinase, the G-subunit of phosphatase-1, ATP-citrate lyase, acetyl coenzyme A carboxylase, myelin basic protein, a microtubule-associated protein, a neurofilament protein, an N-CAM cell adhesion molecule, nerve growth factor receptor, c-Jun  
10 transcription factor, JunD transcription factor, c-Myb transcription factor, c-Myc transcription factor, L-Myc transcription factor, adenomatous polyposis coli tumor suppressor protein, tau protein and  $\beta$ -catenin.

The above-indicated diversity of proteins which may be phosphorylated by GSK3  
15 implies that GSK3 is implicated in numerous metabolic and regulatory processes in cells.

GSK3 inhibitors may therefore be useful in the prevention or treatment of diseases mediated through GSK3 activity such as bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal  
20 dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Down syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with  
25 tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, cancer, dermatological disorders such as baldness, neuroprotection, schizophrenia, pain, in particular neuropathic pain. GSK3 inhibitors can also be used to inhibit sperm  
30 motility and can therefore be used as male contraceptives.

In particular, the compounds of the present invention are useful in the prevention or treatment of Alzheimer's disease, diabetes, especially type 2 diabetes (non insulin dependent diabetes).

35 The major neuropathological landmarks in Alzheimer's disease are neuronal loss, the deposition of amyloid fibers and paired helical filaments (PHF) or neurofibrillary tangles (NFT). Tangle formation appears to be the consequence of accumulation of

- aberrantly phosphorylated tau protein. This aberrant phosphorylation destabilizes neuronal cytoskeleton, which leads to reduced axonal transport, deficient functioning and ultimately neuronal death. The density of neurofibrillary tangles has been shown to parallel duration and severity of Alzheimer's disease. Reduction of the degree of tau phosphorylation can provide for neuroprotection and can prevent or treat Alzheimer's disease or can slow the progression of the disease. As mentioned hereinabove, GSK3 phosphorylates tau protein. Thus compounds having an inhibitory activity for GSK3 may be useful for the prevention or the treatment of Alzheimer's disease.
- 10 Insulin regulates the synthesis of the storage polysaccharide glycogen. The rate-limiting step in the glycogen synthesis is catalyzed by the enzyme glycogen synthase. It is believed that glycogen synthase is inhibited by phosphorylation and that insulin stimulates glycogen synthase by causing a net decrease in the phosphorylation of this enzyme. Thus, in order to activate glycogen synthase, insulin must either activate
- 15 phosphatases or inhibit kinases, or both. It is believed that glycogen synthase is a substrate for glycogen synthase kinase 3 and that insulin inactivates GSK3 thereby promoting the dephosphorylation of glycogen synthase. In addition to the role of GSK3 in insulin-induced glycogen synthesis, GSK3 may also
- 20 play a role in insulin resistance. It is believed that GSK3 dependent Insulin Receptor Substrate-1 phosphorylation contributes to insulin resistance. Therefore, GSK3 inhibition may result in the increased deposition of glycogen and a concomitant reduction of blood glucose, thus mimicing the hypoglycemic effect of insulin. GSK3 inhibition provides an alternative therapy to manage insulin resistance
- 25 commonly observed in non insulin dependent diabetes mellitus and obesity. GSK3 inhibitors may thus provide a novel modality for the treatment of type 1 and type 2 diabetes.
- GSK3 inhibitors may also be indicated for use in the prevention or the treatment of
- 30 pain, in particular neuropathic pain. After axotomy or chronic constriction injury, neuronal cells die through an apoptotic pathway and the morphological changes correlate with the onset of hyperalgesia and/or allodynia. The induction of apoptosis is probably triggered by a reduced supply of neurotrophic factors as the time course of neuronal loss is positively altered by administration of
- 35 neurotrophins. GSK has been shown to be involved in the initiation of the apoptotic cascade and trophic factor withdrawal stimulates the GSK3 apoptosis pathway.



In view of the above, GSK3 inhibitors might reduce signals of and even prevent levels of neuropathic pain.

Due to their GSK3 inhibitory properties, the compounds of formula (I), their *N*-oxides,  
5 pharmaceutically acceptable addition salts, quaternary amines and stereochemically  
isomeric forms thereof, are useful to prevent or treat GSK3 mediated diseases, such as  
bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease,  
leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease),  
cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy,  
10 Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with  
tangles only, dementia with tangles and calcification, Down syndrome, myotonic  
dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia,  
Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing  
panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute  
15 sclerotizing panencephalitis (SSPE) ( late complication of viral infections in the central  
nervous system), inflammatory diseases, cancer, dermatological disorders such as  
baldness, neuroprotection, schizophrenia, pain, in particular neuropathic pain. The  
present compounds are also useful as male contraceptives. In general, the compounds  
of the present invention may be useful in the treatment of warm-blooded animals  
20 suffering from disease mediated through GSK3, in particular GSK3 $\beta$ , or they may be  
useful to prevent warm-blooded animals to suffer from disease mediated through  
GSK3, in particular GSK3 $\beta$ . More in particular, the compounds of the present  
invention may be useful in the treatment of warm-blooded animals suffering from  
Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases  
25 or bipolar disorder.

In view of the above described pharmacological properties, the compounds of formula  
(I) or any subgroup thereof, their *N*-oxides, pharmaceutically acceptable addition salts,  
quaternary amines and stereochemically isomeric forms, may be used as a medicine. In  
30 particular, the present compounds can be used for the manufacture of a medicament for  
treating or preventing diseases mediated through GSK3. More in particular, the present  
compounds can be used for the manufacture of a medicament for treating or preventing  
Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases  
or bipolar disorder.

35

In view of the utility of the compounds of formula (I), there is provided a method of  
treating warm-blooded animals, including humans, suffering from or a method of

preventing warm-blooded animals, including humans, to suffer from diseases mediated through GSK3, more in particular a method of treating or preventing Alzheimer's disease, diabetes, especially type 2 diabetes, cancer, inflammatory diseases or bipolar disorder. Said method comprises the administration, preferably oral administration, of  
5 an effective amount of a compound of formula (I), a *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for preventing or treating diseases  
10 mediated through GSK3, comprising a therapeutically effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier or diluent.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate  
15 compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of  
20 preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of  
25 oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are  
30 obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case  
35 appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous

administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be  
5 helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention  
10 may be administered to the lungs in the form of a solution, a suspension or a dry powder. Any system developed for the delivery of solutions, suspensions or dry powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

15 It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required  
20 pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

The present compounds are orally active compounds, and are preferably orally  
25 administered.

The exact dosage, the therapeutically effective amount and frequency of administration depends on the particular compound of formula (I) used, the particular condition being treated, the severity of the condition being treated, the age, weight, sex, extent of disorder and general physical condition of the particular patient as well as other  
30 medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention.

35 When used as a medicament to prevent or treat Alzheimer's disease, the compounds of formula (I) may be used in combination with other conventional drugs used to combat Alzheimer's disease, such as galantamine, donepezil, rivastigmine or tacrine.

Thus, the present invention also relates to the combination of a compound of formula (I) and another agent capable of preventing or treating Alzheimer's disease. Said combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I), and (b) another agent capable of preventing or treating Alzheimer's disease, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of Alzheimer's disease. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

10 When used as a medicament to prevent or treat type 2 diabetes, the compounds of formula (I) may be used in combination with other conventional drugs used to combat type 2 diabetes, such as glibenclamide, chlorpropamide, gliclazide, glipizide, gliquidon, tolbutamide, metformin, acarbose, miglitol, nateglinide, repaglinide, acetohexamide, glimepiride, glyburide, tolazamide, troglitazone, rosiglitazone, pioglitazone, 15 isaglitazone.

Thus, the present invention also relates to the combination of a compound of formula (I) and another agent capable of preventing or treating type 2 diabetes. Said combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I), and (b) another agent capable of preventing or treating type 2 diabetes, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of type 2 diabetes. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

25 When used as a medicament to prevent or treat cancer, the compounds of formula (I) may be used in combination with other conventional drugs used to combat cancer such as platinum coordination compounds for example cisplatin or carboplatin; taxane compounds for example paclitaxel or docetaxel; camptothecin compounds for example irinotecan or topotecan; anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine; anti-tumour nucleoside derivatives for example 5-fluorouracil, 30 gemcitabine or capecitabine; nitrogen mustard or nitrosourea alkylating agents for example cyclophosphamide, chlorambucil, carmustine or lomustine; anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin or idarubicin; HER2 antibodies for example trastuzumab; and anti-tumour podophyllotoxin derivatives for example etoposide or teniposide; and antiestrogen agents including estrogen receptor antagonists or selective estrogen receptor modulators preferably tamoxifen, or 35 alternatively toremifene, droloxifene, faslodex and raloxifene; aromatase inhibitors

such as exemestane, anastrozole, letrozole and vorozole; differentiating agents for example retinoids, vitamin D and DNA methyl transferase inhibitors for example azacytidine; kinase inhibitors for example flavoperidol and imatinib mesylate or farnesyltransferase inhibitors for example R115777.

- 5 Thus, the present invention also relates to the combination of a compound of formula (I) and another agent capable of preventing or treating cancer. Said combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I), and (b) another agent capable of preventing or treating cancer, as a combined preparation for simultaneous, separate or sequential use in the  
10 prevention or treatment of cancer. The different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

- When used as a medicament to prevent or treat bipolar disorder, the compounds of formula (I) may be used in combination with other conventional drugs used to combat  
15 bipolar disorder such as atypical antipsychotics, anti-epileptics, benzodiazepines, lithium salts, for example olanzapine, risperidone, carbamazepine, valproate, topiramate.

- Thus, the present invention also relates to the combination of a compound of formula (I) and another agent capable of preventing or treating bipolar disorder. Said  
20 combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I), and (b) another agent capable of preventing or treating bipolar disorder, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of bipolar disorder. The different drugs may be combined in a single preparation together with pharmaceutically acceptable  
25 carriers.

- When used as a medicament to prevent or treat inflammatory diseases, the compounds of formula (I) may be used in combination with other conventional drugs used to combat inflammatory diseases such as steroids, cyclooxygenase-2 inhibitors, non-  
30 steroidal-anti-inflammatory drugs, TNF-  $\alpha$  antibodies, such as for example acetyl salicylic acid, bufexamac, diclofenac potassium, sulindac, diclofenac sodium, ketorolac trometamol, tolmetine, ibuprofen, naproxen, naproxen sodium, tiaprofen acid, flurbiprofen, mefenamic acid, niflumonic acid, meclofenamate, indomethacin, proglumetacine, ketoprofen, nabumetone, paracetamol, piroxicam, tenoxicam,  
35 nimesulide, fenylbutazon, tramadol, beclomethasone dipropionate, betamethasone, beclomethasone, budesonide, fluticasone, mometasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone,

celecoxib, rofecoxib, infliximab, leflunomide, etanercept, CPH 82, methotrexate, sulfasalazine.

Thus, the present invention also relates to the combination of a compound of formula (I) and another agent capable of preventing or treating inflammatory diseases. Said  
5 combination may be used as a medicine. The present invention also relates to a product containing (a) a compound of formula (I), and (b) another agent capable of preventing or treating inflammatory diseases, as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of inflammatory disorders. The  
10 different drugs may be combined in a single preparation together with pharmaceutically acceptable carriers.

The following examples illustrate the present invention.

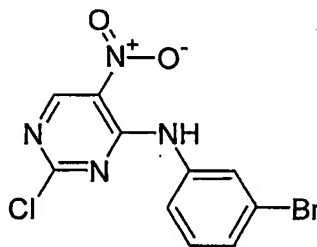
#### Experimental part

15 Hereinafter, "DMF" is defined as *N,N*-dimethylformamide, "DIPE" is defined as diisopropylether, "DMSO" is defined as dimethylsulfoxide, "THF" is defined as tetrahydrofuran, "DMA" is defined as *N,N*-dimethylacetamide and "DIPEA" is defined as diisopropylethylamine.

#### 20 A. Preparation of the intermediate compounds

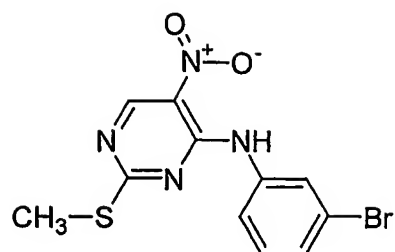
##### Example A1

##### a. Preparation of intermediate 1



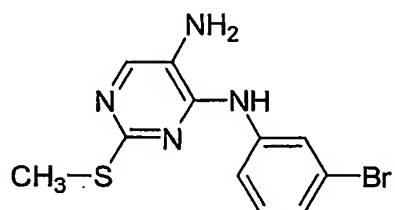
A mixture of 2,4-dichloro-5-nitropyrimidine (0.05 mol) in DMA (400 ml) was cooled to -20 °C and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.05 mol) was added, then a  
25 mixture of 3-bromo-benzeneamine (0.05 mol) in DMA (200 ml) was added dropwise at -20 °C and the reaction mixture was stirred at -20 °C for 2 hours. The reaction mixture containing intermediate 1 was used as such in the next reaction step.

b. Preparation of intermediate 2



NaSCH<sub>3</sub>, 21% in H<sub>2</sub>O (0.05 mol) was added dropwise to intermediate 1 (0.05 mol) and the reaction mixture was stirred for 1.5 hour at room temperature, then the mixture was carefully poured out into H<sub>2</sub>O. The resulting precipitate was stirred over the weekend, filtered off, washed and dried (vacuum). Yield: 15.73 g (92.5 %). The product was crystallised from CH<sub>3</sub>CN, then the resulting precipitate was filtered off, washed and dried (vacuum). Yield: intermediate 2.

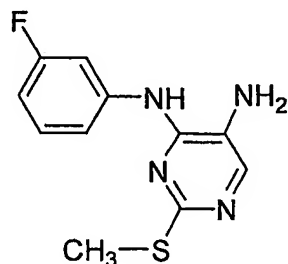
c. Preparation of intermediate 3

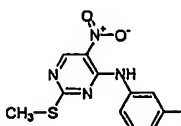


A mixture of intermediate 2 (0.028 mol) in CH<sub>3</sub>OH (250 ml) was hydrogenated with Pt/C 5% (2g) as a catalyst in the presence of a solution of thiophene in DIPE (4% v/v, 1 ml). After uptake of H<sub>2</sub> (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. The residue was crystallised from CH<sub>3</sub>CN, then the resulting precipitate was filtered off, washed and dried (vacuum). Yield: 5.2 g of intermediate 3.

Example A2

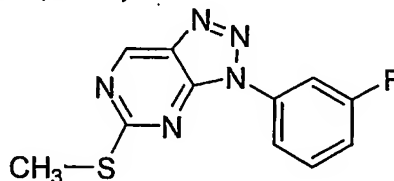
a. Preparation of intermediate 4



A mixture of  (prepared according to A1.b) (0.07 mol) and Et<sub>3</sub>N (10 g) in THF (250 ml) was hydrogenated with Pd/C, 10% (5 g) as a catalyst in the presence of a solution of thiophene in DIPE (4% v/v, 5 ml). After uptake of H<sub>2</sub> (3 equiv), the catalyst was filtered off and the filtrate was evaporated. The residue was stirred in DIPE with a small amount of CH<sub>3</sub>CN. The precipitate was filtered off and dried. Yield: 12.3 g of intermediate 4 (70.2%). The filtrate was acidified with HCl/2-propanol while

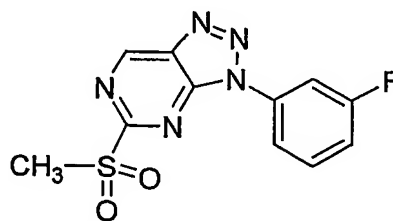
stirring. The mixture was stirred for 30 minutes. The resulting precipitate was filtered off and dried. Yield: 5.17 g of intermediate 4 (25.7%).

b. Preparation of intermediate 5



- Intermediate 4 (0.08 mol) was dissolved in a mixture of 6N HCl (400 ml) and HOAc, p.a. (400 ml) and the whole was cooled to 0-5 °C. A solution of NaNO<sub>2</sub> (0.1 mol) in H<sub>2</sub>O (40 ml) was added dropwise over a 30 minutes period. Then, the reaction mixture was stirred for another 30 minutes while cooling on the ice-bath. Then, the mixture was stirred overnight at room temperature. The resulting precipitate was filtered off, rinsed with water, with 2-propanone, then with DIPE, and dried. Yield: 18.14 g of intermediate 5 (87%).

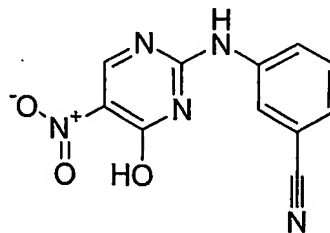
c. Preparation of intermediate 6



- Intermediate 5 (15 g, 0.058 mol) was stirred in HOAc (700 ml) and cooled on an ice-bath. A solution of KMnO<sub>4</sub>, p.a. (24 g, 0.15 mol) in demineralized H<sub>2</sub>O (300 ml) was added dropwise over a 60 minutes period while cooling on an ice-bath. The mixture was stirred for one hour on the ice-bath, then for 2 hours at room temperature. Sodium bisulfite was added until a colour change resulted. EtOAc was added while stirring vigorously for a while. The mixture was stood overnight. The mixture was concentrated to ± 50-ml volume. The aqueous concentrate was stirred for a while and the resulting precipitate was filtered off and dried. Yield: 11.023 g of intermediate 6 (64.8%).

Example A3

a. Preparation of intermediate 7

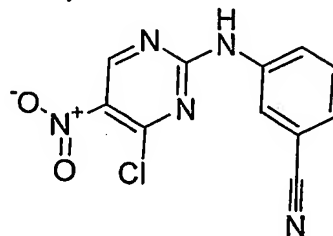


- A mixture of 2-chloro-5-nitro-4(1*H*)-Pyrimidinone (0.005 mol) and 3-amino-benzonitrile (0.005 mol) in 2-methoxyethanol (25 ml, p.a.) was stirred for 3 hours at 100-110 °C. The solvent was evaporated and the residue was stirred in



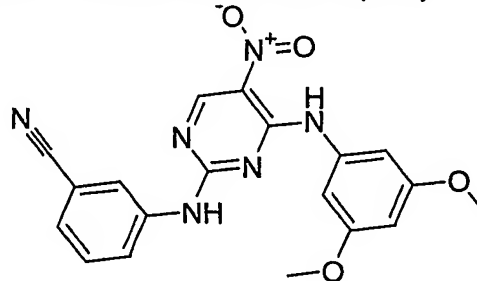
CH<sub>3</sub>CN with a small amount of CH<sub>3</sub>OH. The resulting precipitate was filtered off and dried. Yield: 1.300 g of intermediate 7 (100 %).

b. Preparation of intermediate 8



5 A mixture of intermediate 7 (0.006 mol) in POCl<sub>3</sub> (15 ml) was stirred for 2 hours at 95 °C, then the reaction mixture was stirred overnight at room temperature. The solvent was evaporated and the residue was stirred in 2-propanol/H<sub>2</sub>O/CH<sub>3</sub>OH. The resulting precipitate was filtered off and dried. Yield: 1.143 g of intermediate 8 (69%).

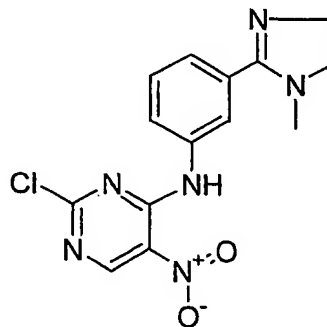
c. Preparation of intermediate 9



10 A mixture of 3,5-dimethoxybenzenamine (0.001 mol) and intermediate 8 (0.001 mol) in ethanol (20 ml) was heated to reflux ( $\pm$  10 minutes) and the reaction mixture was stirred overnight at room temperature. The resulting precipitate was filtered off and dried. Yield: 0.327 g of intermediate 9 (83 %).

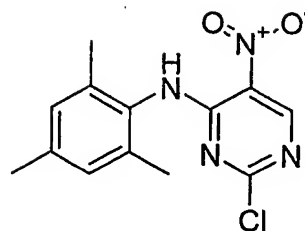
Example A4

a. Preparation of intermediate 10



15 A solution of 2,4-dichloro-5-nitropyrimidine (0.0127 mol) in DMF (60 ml) was stirred at 0 °C. *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.0127 mol) was added. A solution of 3-(1-methyl-1*H*-imidazol-2-yl)benzenamine (0.0127 mol) in DMF (20 ml) was added dropwise and the resulting reaction mixture was stirred for one hour at 0°C, then overnight at room temperature. The reaction mixture containing intermediate 10 was used as such in the next reaction step.

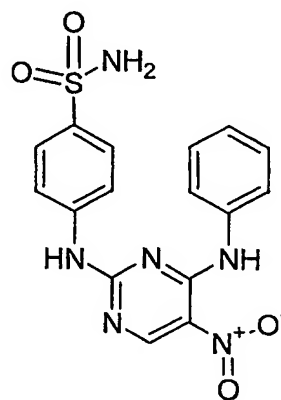
b. Preparation of intermediate 11



2,4,6-Trimethylbenzenamine (0.0259 mol), 2,4-dichloro-5-nitropyrimidine (0.0259 mol) and 1,4-dioxane (25 ml) were combined in a RB flask equipped with stirbar and reflux condenser under Ar and heated to reflux for 16 hours. The sample was concentrated by rotary evaporation onto silica gel and purified by column chromatography twice (Biotage 40M, 1:1 hexanes: methylene chloride, second purification: eluent: 25%--> 40% methylene chloride in hexanes) to give intermediate 11.

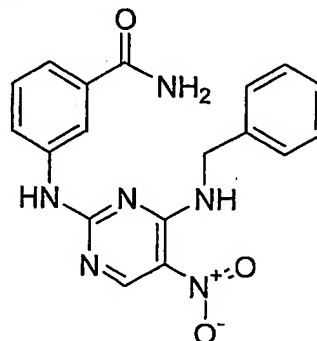
Example A5

a. Preparation of intermediate 12



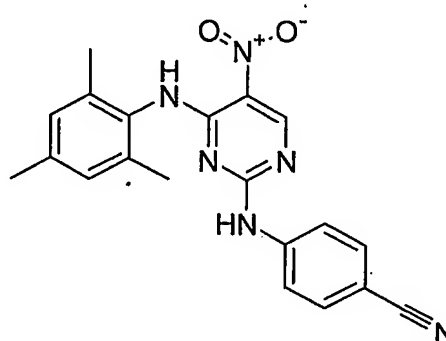
4-Aminobenzenesulfonamide (0.046 mol) was added to a solution of *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (6 g) in 2-chloro-5-nitro-*N*-phenyl-4-pyrimidinamine (153 ml) and the reaction mixture was heated overnight at 60 °C, then the mixture was added dropwise to ice-water (500 ml). The resulting solids were filtered off and dried in a vacuum oven at 60 °C, then suspended in DIPE/CH<sub>3</sub>OH. The suspension was recrystallised from diglyme (diethylene glycol dimethyl ether) and the resulting solids were collected. Yield: 4.7 g of intermediate 12.

b. Preparation of intermediate 13



A solution of 2-chloro-5-nitro-*N*-(phenylmethyl)-4-pyrimidinamine (0.012 mol), 3-aminobenzamide (0.012 mol) and *N,N*-diethylethanamine (0.012 mol) in DMF (50 ml) was stirred for 2 hours at 60 °C. The mixture was allowed to cool to room temperature and methanol (10 ml) was added. The mixture was stirred for 10 minutes and the resulting precipitate was filtered off, washed and dried. Yield: 3.3 g of intermediate 13 (77%).

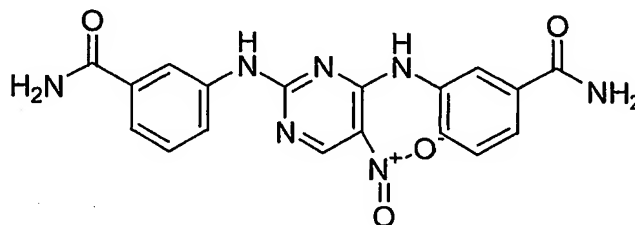
c. Preparation of intermediate 14



Intermediate 11 (0.0547 mol), 4-aminobenzonitrile (0.01367 mol) and 1,4-dioxane (30 ml) were combined and heated to 60 °C for 4 days. 1,4-Dioxane was removed by rotary evaporation. The pH of the reaction mixture was adjusted to > 10 using 1 N NaOH. CH<sub>2</sub>Cl<sub>2</sub> was added to the reaction mixture, the resulting emulsion was filtered and the yellow solid was washed with copious methylene chloride to give intermediate 14.

Example A6

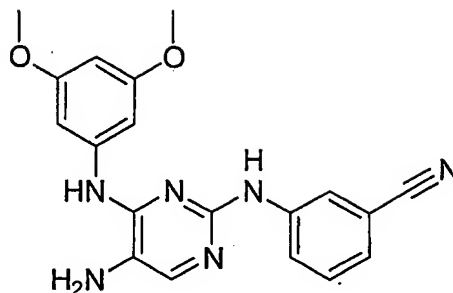
Preparation of intermediate 15



A mixture of 2,4-dichloro-5-nitropyrimidine (0.038 mol) in CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was cooled to 0°C and *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.038 mol) was added. A solution of 3-aminobenzamide (0.038 mol) in DMF (30 ml) was added dropwise. Then the reaction mixture was allowed to warm to room temperature and was stirred for the weekend. The formed precipitate was filtered off and washed. The filtrate was concentrated. Yield : 2.7g of intermediate 15.

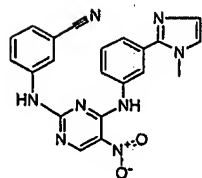
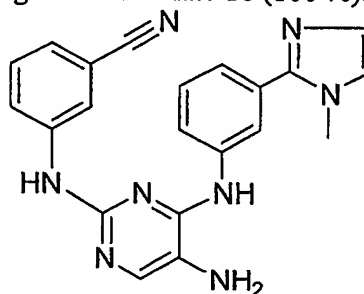
Example A7

a. Preparation of intermediate 16



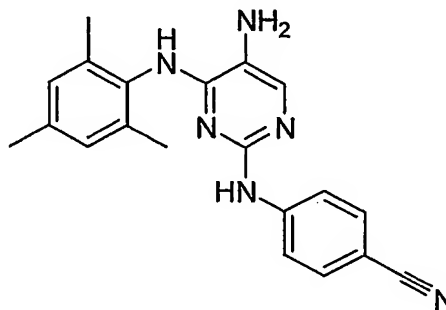
- 5 A mixture of intermediate 9 (0.0008 mol) in ethanol (40 ml) was hydrogenated with Pt/C 5% (0.050 g) as a catalyst in the presence of a solution of thiophene in DIPE (4%v/v, 0.05 ml). After uptake of hydrogen (3 equiv.), the catalyst was filtered off and the filtrate was evaporated. Yield: 1 0.5 g of intermediate 16 (100 %).

b. Preparation of intermediate 17



- (0.0127 mol; prepared from intermediate 10 (A4a.) according to A5a.-A5b.) in DMF (80 ml) was hydrogenated at room temperature with Pd/C 10% (2g) as a catalyst in the presence of a solution of thiophene in DIPE (4% v/v, 2ml). After uptake of hydrogen (3 equiv), the catalyst was filtered off and the solvent was evaporated.
- 10 Yield: intermediate 17.

c. Preparation of intermediate 18

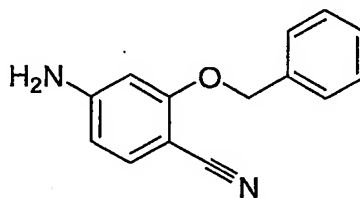


Intermediate 14 (0.001 mol), Pd/C 10% (0.025 g), ethanol (20 ml), and  $\text{NH}_2\text{-NH}_2$  (0.030 mol) were combined to form a slurry and stirred at room temperature for 16 hours. The solvent was removed by rotary evaporation. The residue was taken up in

THF (20 ml) and methanol (1 ml). A second portion of  $\text{NH}_2\text{-NH}_2$  (0.5 g) was added, and the reaction was stirred for 16 hours at room temperature. A third portion of  $\text{NH}_2\text{-NH}_2$  (0.5 ml) was added and the reaction was stirred for an additional 16 hours at room temperature. The sample was concentrated by rotary evaporation onto silica gel (1 g) and purified by flash chromatography (Biotage 40S, eluent: 0.5, 1, 2 % 10% ( $\text{NH}_4\text{OH}$  in  $\text{CH}_3\text{OH}$ ) in  $\text{CH}_2\text{Cl}_2$ ) to give a solid. Trituration with a variety of solvents was done and the portions were recombined and purified by preparatory HPLC to give the final solid after the combined HPLC fractions were lyophilized. Yield: 0.24 g of intermediate 18 (70%).

10 Example A8

a. Preparation of intermediate 19

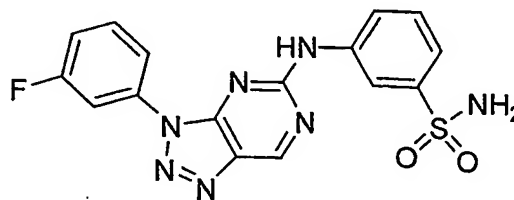


A mixture of Fe (0.12 mol) in 0.78 N  $\text{NH}_4\text{Cl}$  solution (70 ml) was stirred at reflux temperature. 4-nitro-2-(phenylmethoxy)benzonitrile (0.047 mol) was added in small portions. The resultant reaction mixture was stirred and refluxed for 4 hours, then cooled, filtered and the residue was extracted on Soxhlet with toluene. The extract's solvent was evaporated. The residue was dried in vacuo. Yield: 8.2 g of intermediate 19 (78%).

B. Preparation of the final compounds

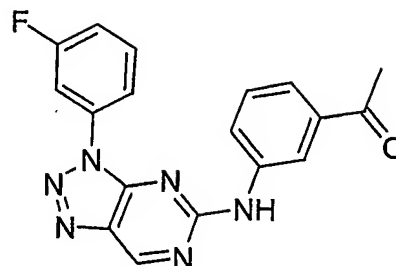
Example B1

a. Preparation of compound 1



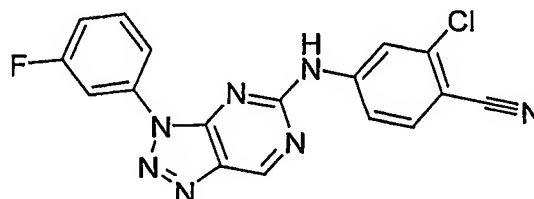
20 A mixture of intermediate 6 (0.00034 mol) and 3-aminobenzenesulfonamide (0.00034 mol) in DMSO (2 ml) was stirred overnight at 100 °C, then  $\text{H}_2\text{O}$  and  $\text{CH}_3\text{CN}$  were added and the reaction mixture was warmed. The resulting precipitate was filtered off, washed and dried (vacuum). Yield: 0.032 g of compound 1 (m.p. 177 °C)

b. Preparation of compound 2



A mixture of intermediate 6 (0.001 mol) and 1-(3-aminophenyl)ethanone (0.002 mol) in 2-methoxyethanol (10 ml) was stirred and refluxed for 16 hours and the solution was cooled. The resulting precipitate was filtered off, rinsed with EtOH/DIPE and dried. Yield: 0.250 g of compound 2 (72 %, m.p. 220-224°C). The filtrate was evaporated and the residue was stirred in CH<sub>3</sub>CN/CH<sub>3</sub>OH (2ml/2ml). The mixture was stirred for a while, then the precipitate was filtered off and dried. Yield: 0.098 g of compound 2 (28%).

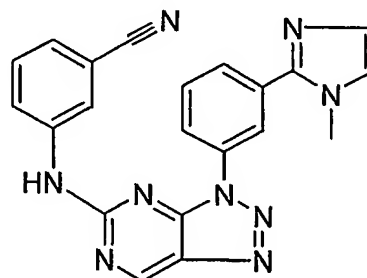
c. Preparation of compound 3



A mixture of 4-amino-2-chlorobenzonitrile (0.00034 mol) and NaH (0.00034 mol) in *N,N*-dimethylformamide (3 ml) was stirred at room temperature for 1 hour and intermediate 6 (0.00034 mol) was added, then the reaction mixture was stirred overnight at room temperature. H<sub>2</sub>O and CH<sub>3</sub>CN were added and the mixture was heated until complete dissolution, then stirred at room temperature for a few hours. The resulting precipitate was filtered off, washed and dried (vacuum). Yield: 0.0275 g of compound 3 (m.p.: >260 °C).

Example B2

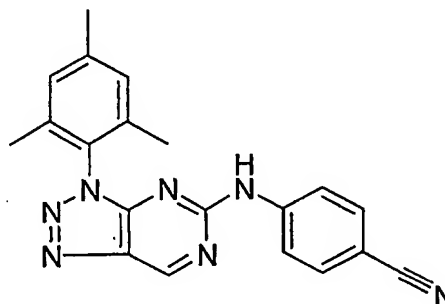
a. Preparation of compound 4



Intermediate 17 (0.0127 mol) in HCl 6N (50ml) was cooled to 0°C. Sodium nitrite (0.015 mol) in water (10 ml) was added dropwise. The mixture was stirred at room temperature for 18 hours; then neutralized with a NaOH solution. The formed precipitate was filtered off, washed and dried. Yield : 4.2g. This fraction was dissolved in MeOH/HCl/H<sub>2</sub>O. The precipitate was filtered off. The filtrate was purified by high

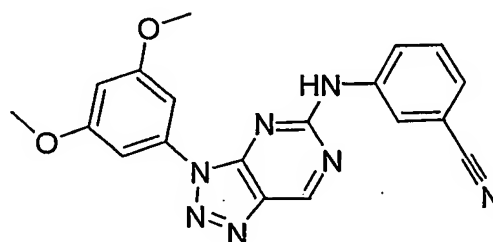
performance liquid chromatography over hyperprep C18 BDS (eluent: (0.5% NH<sub>4</sub>OAc in H<sub>2</sub>O/CH<sub>3</sub>CN)/MeOH/CH<sub>3</sub>CN 75/25/0;0/50/50;0/0/100). The desired fractions were collected and the solvent was evaporated. The residue was stirred in DIPE. The precipitate was filtered off, washed and dried (vacuum;50°C). Yield : 0.22g of compound 4.

b. Preparation of compound 5



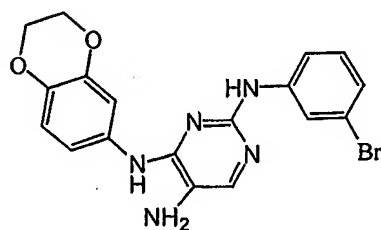
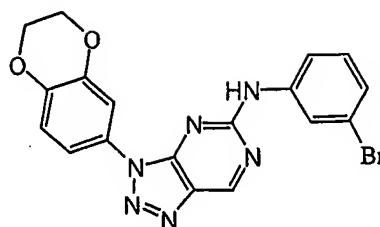
Sodium nitrite (0.00290 mol) was added to intermediate 18 (0.00290 mol) in concentrated HCl (60 ml). The mixture was stirred at room temperature for 4 hours. The sample was cooled in an ice-bath and free based with solid NaOH. A solid was collected by filtration. This solid was air dried for 2.5 days. The sample was adsorbed onto silica gel (2.0 g) and purified by column chromatography (Biotage 40 M, eluent 10%, 50%, 60% EtOAc in hexanes). The desired fractions were rotary evaporated to a solid which was dried at room temperature in vacuo for 18 hours to yield 0.56 g of compound 5 (54%).

c. Preparation of compound 6



Intermediate 16 (0.0008 mol) was stirred in HCl 6N (10 ml) and acetic acid (10 ml) at room temperature. A solution of sodium nitrite (0.0010 mol) in water (1 ml) was added dropwise and the reaction mixture was stirred for 1 hour. The precipitate was filtered off, washed with H<sub>2</sub>O, with CH<sub>3</sub>OH and with DIPE and then dried. Yield: 0.184 g of compound 6 (62 %, m.p.: 228-232 °C).

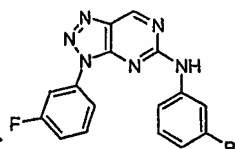
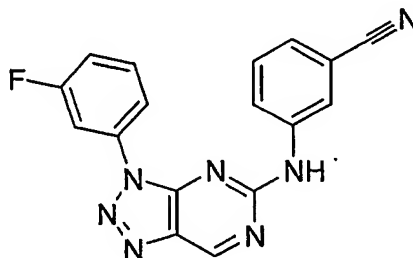
d. Preparation of compound 46



(prepared according to A7a) (0.00022 mol) was suspended in HOAc (5 ml). HCl, 6N (1.1 ml; 30 equiv.) was added and the mixture was cooled to 0°C. A solution of NaNO<sub>2</sub> (0.000275 mol; 1.25 equiv.) in H<sub>2</sub>O (0.5 ml) was added slowly, dropwise. The reaction mixture was stirred for 1 hour at 0°C, then for 1 hour at room temperature. The mixture was evaporated. The residue was triturated under water and some 2-propanone, filtered, washed with water on the funnel, then dried. Yield : 0.060 g of compound 46 (64%).

Example B3

Preparation of compound 8



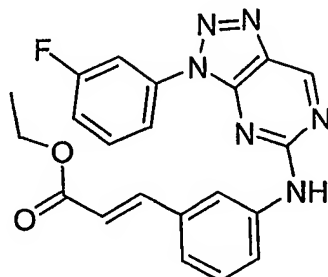
- 10 A mixture of (compound 7; prepared according to B1b) (0.00052 mol), tris(dibenzylideneacetone)dipalladium (0.025 g), 1,1'-bis(diphenylphosphino)ferrocene (0.033 g) and Zn + Zn (CN)<sub>2</sub> (0.012 g + 0.105 g) in DMA (10 ml) was reacted according to the following procedure. The reaction mixture was reacted in a microwave for 15 minutes at 150 °C, then the mixture was filtered over dicalite and washed thoroughly with DMF. The solvent was evaporated and the residue was stirred in CH<sub>3</sub>CN. The resulting precipitate was filtered off and dried. This fraction was purified over silica gel (eluent: CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH 98/2). The product fractions were collected and the solvent was evaporated. The residue was stirred in



DIPE/CH<sub>3</sub>CN (1/1), then the resulting precipitate was filtered off and dried. Yield: 0.127 g of compound 8 (73 %, m.p.: 228-230 °C).

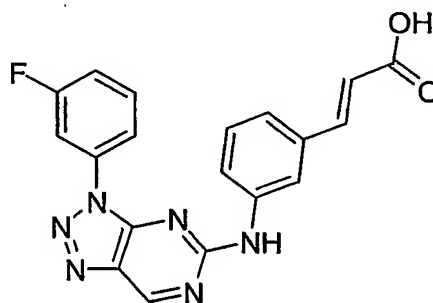
Example B4

a. Preparation of compound 9



- 5 A mixture of compound 7 (0.0013 mol), ethyl 2-propenoate (0.025 mol), Pd(OAc)<sub>2</sub> (0.0002 mol) and 1,3-bis(diphenylphosphino)propane (0.0004 mol) in *N,N*-diethylethanamine (3 ml) and THF (100 ml) was stirred for 16 hours in autoclave at 125 °C, the solvent was evaporated and the residue was stirred in boiling CH<sub>3</sub>CN. The precipitate was filtered off and dried. Yield: 0.374 g of compound 9 (71 %, m.p.: 216 °C).

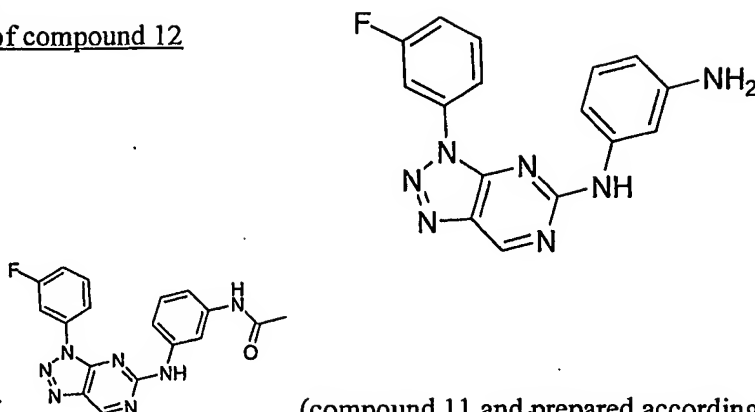
b. Preparation of compound 10



- 10 A mixture of compound 9 (0.001 mol) and NaOH 1N (0.015 mol) in THF (35 ml) was stirred for 20 hours at room temperature, then the reaction mixture was stirred for 4 hours at 60 °C and the solution was stirred overnight at room temperature. The organic solvent (THF) was evaporated, the aqueous concentrate was diluted with H<sub>2</sub>O (20 ml) and neutralised with HCl (15 ml, 1N). The mixture was stirred for a few hours and the
- 15 resulting precipitate was filtered off. This fraction was taken up in H<sub>2</sub>O/DMSO and NaOH (10 ml, 1N) was added, then the mixture was warmed until complete dissolution, filtered over a pleated paper filter and cooled. The residue was washed 5 times with EtOAc and the aqueous layer was neutralised with HCl (10 ml, 1N). The mixture was stirred overnight, then the resulting precipitate was filtered off and dried
- 20 (vacuum). Yield: 0.202 g of compound 10 (54 %, m.p.: > 250 °C).

Example B5

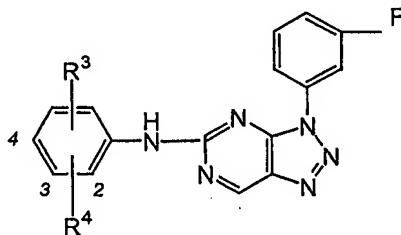
Preparation of compound 12



A mixture of (compound 11 and prepared according to B1b) (0.00019 mol) in HCl 12N (2 ml) and ethanol (3 ml) was stirred for 2 hours at 90 °C, then the reaction mixture was cooled and the solvent was evaporated. The residue was crystallised from CH<sub>3</sub>OH, the resulting precipitate was filtered off and dried. Yield: 0.027 g of compound 12 (m.p.: 224 °C)

Tables 1 to 3 list the compounds of formula (I) which were prepared according to one of the above examples.

Table 1

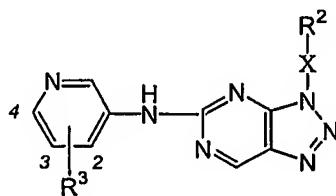


Co. no.	Ex. no.	R <sup>3</sup>	R <sup>4</sup>	physical data (m.p. °C /salt)
1	B1a	3-[SO <sub>2</sub> -NH <sub>2</sub> ]	H	177°C
2	B1b	3-[CO-CH <sub>3</sub> ]	H	222
3	B1c	3-Cl	4-CN	>260°C
7	B1b	3-Br	H	221
8	B3	3-CN	H	228-230°C
9	B4a	3-[CH=CH-CO-O-C <sub>2</sub> H <sub>5</sub> ]	H	216°C
10	B4b	3-[CH=CH-CO-OH]	H	>250°C
11	B1b	3-[NH-CO-CH <sub>3</sub> ]	H	224°C
12	B5	3-NH <sub>2</sub>	H	224°C / HCl
13	B1b	3-[CO-O-CH <sub>3</sub> ]	H	

Co. no.	Ex. no.	R <sup>3</sup>	R <sup>4</sup>	physical data (m.p. °C/salt)
14	B1b	3-CH <sub>3</sub>	H	
15	B1b	3-OH	H	>260
16	B1b	3-Cl	5-Cl	
17	B1b	3-F	H	192
18	B1b	4-[S-CN]	H	
19	B1b	4-[O-CHF <sub>2</sub> ]	H	
20	B1b	4-[CH <sub>2</sub> -CN]	H	
21	B1b	3-OH	4-CH <sub>3</sub>	174
22	B1b	3-[O-CF <sub>3</sub> ]	H	
23	B1b	3-[O-C <sub>2</sub> H <sub>5</sub> ]	H	167
24	B1a	3-[CO-NH-CH <sub>3</sub> ]	H	
25	B1b	3-[CH <sub>2</sub> -COOH]	H	240
26	B1b	2-[CH <sub>2</sub> -OH]	H	234
27	B1b	3-[CH(OH)-CH <sub>3</sub> ]	H	152
28	B1b	3-[O-CH(CH <sub>3</sub> ) <sub>2</sub> ]	H	144
29	B1a	3-COOH	H	>260
30	B1a	4-COOH	H	>260
31	B1a	3-[CH <sub>2</sub> -OH]	H	190

m.p. = melting point

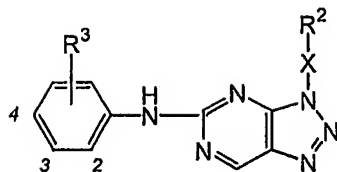
Table 2

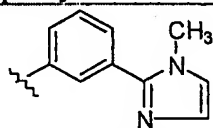
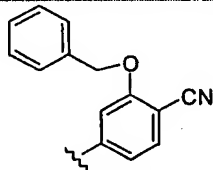
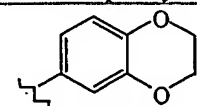


Co. no.	Ex. no.	R <sup>3</sup>	X-R <sup>2</sup>	physical data (m.p. °C/salt)
32	B1b	4-Cl	3-fluorophenyl	
47	B1b.	4-OCH <sub>3</sub>	phenyl	202

m.p.= melting point

Table 3



Co. no.	Ex. no.	R <sup>3</sup>	X	R <sup>2</sup>	physical data (m.p. °C / salt)
33	B1a	3-CN	db	3-bromophenyl	252
6	B2c	3-CN	db	3,5-dimethoxyphenyl	228-232°C / ½ C <sub>2</sub> H <sub>4</sub> O <sub>2</sub>
34	B2c	3-CN	db	phenyl	192
4	B2a	3-CN	db		
5	B2b	4-CN	db	2,4,6-trimethylphenyl	
35	B1b	3-[SO <sub>2</sub> -NH <sub>2</sub> ]	db	3-methoxyphenyl	222
36	B1b	3-[SO <sub>2</sub> -NH <sub>2</sub> ]	db	3-(hydroxymethyl)phenyl	224
37	B2c	4-[SO <sub>2</sub> -NH <sub>2</sub> ]	db	phenyl	288
38	B2c	3-[CO-NH <sub>2</sub> ]	db	phenyl	
39	B2c	3-[CO-NH <sub>2</sub> ]	db	3-(aminocarbonyl)phenyl	
40	B2c	3-[CO-NH <sub>2</sub> ]	db		
41	B2c	3-[CO-NH <sub>2</sub> ]	CH <sub>2</sub>	phenyl	
42	B1b	3-[NH-CO-CH <sub>3</sub> ]	db	3-methoxyphenyl	216
43	B1b	3-[CH(OH)-CH <sub>3</sub> ]	db	3-methoxyphenyl	128
44	B1b	3-[SO <sub>2</sub> -CH <sub>3</sub> ]	db	3-fluorophenyl	216
45	B1b	3-[NHSO <sub>2</sub> -CH <sub>3</sub> ]	db	3-fluorophenyl	216
46	B2d	3-Br	db		

### C. Pharmacological Example

The pharmacological activity of the present compounds was examined using the following test.

- 5 GSK3 $\beta$  assays were performed at 25°C in a 100  $\mu$ l reaction volume of 25mM Tris (pH 7.4) containing 10 mM MgCl<sub>2</sub>, 1 mM DTT, 0.1 mg/ml BSA, 5% glycerol and containing 19 nM GSK3 $\beta$ , 5  $\mu$ M biotinylated phosphorylated CREB peptide , 1  $\mu$ M ATP, 2nM ATP-P<sup>33</sup> and a suitable amount of a test compound of formula (I). After one hour, the reaction was terminated by adding 70  $\mu$ l of Stop mix (1 mM ATP, 18 mg/ml streptavidin coated PVT SPA bead pH 11.0). The beads to which the phosphorylated CREB peptide is attached were allowed to settle for 30 minutes and the radioactivity of the beads was counted in a microtiterplate scintillation counter and compared with the results obtained in a control experiment (without the presence of a test compound) in order to determine the percentage of GSK3 $\beta$  inhibition. The IC<sub>50</sub> value, i.e. the concentration (M) of the test compound at which 50 % of GSK3 $\beta$  is inhibited, was calculated from the dose response curve obtained by performing the above-described GSK3 $\beta$  assay in the presence of different amounts of the test compound.
- 15 Table 4 lists ranges (namely pIC<sub>50</sub> >8; pIC<sub>50</sub> ranging between 7 and 8; pIC<sub>50</sub> <7) of pIC<sub>50</sub> values (-log IC<sub>50</sub> (M)) obtained in the above-described test for the present compounds.
- 20

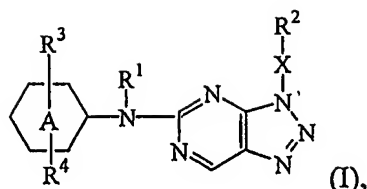
Table 4

Comp. No.	pIC <sub>50</sub>
1	>8
2	>8
3	>8
7	>8
8	>8
9	>8
10	>8
13	7-8
14	7-8
15	>8
17	7-8
18	7-8
19	7-8

Comp. No.	pIC <sub>50</sub>
20	7-8
21	>8
22	>8
23	>8
24	>8
29	>8
30	>8
31	>8
32	>8
33	>8
6	>8
4	>8
37	>8
38	>8
39	>8

# Claims

1. A compound of formula



a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl;

$R^1$  represents hydrogen; aryl; formyl;  $C_{1-6}$ alkylcarbonyl;  $C_{1-6}$ alkyl;

$C_{1-6}$ alkyloxycarbonyl;  $C_{1-6}$ alkyl substituted with formyl,  $C_{1-6}$ alkylcarbonyl,

$C_{1-6}$ alkyloxycarbonyl,  $C_{1-6}$ alkylcarbonyloxy; or  $C_{1-6}$ alkyloxy $C_{1-6}$ alkylcarbonyl

optionally substituted with  $C_{1-6}$ alkyloxycarbonyl;

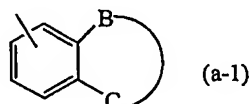
X represents a direct bond;  $C_{1-4}$ alkyl- or  $-C_{1-2}$ alkyl- $X_a$ - $X_b$ ;

with  $X_a$  representing O or  $NR^5$ ; and

with  $X_b$  representing a direct bond or  $C_{1-2}$ alkyl;

$R^2$  represents  $C_{3-7}$ cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic

heterocycle containing at least one heteroatom selected from O, S or N; or a radical of formula



wherein  $-B-C-$  represents a bivalent radical of formula

$-CH_2-CH_2-CH_2-$  (b-1);

$-CH_2-CH_2-CH_2-CH_2-$  (b-2);

$-X_1-CH_2-CH_2-(CH_2)_n-$  (b-3);

$-X_1-CH_2-(CH_2)_n-X_1-$  (b-4);

$-X_1-(CH_2)_n-CH=CH-$  (b-5);

with  $X_1$  representing O or  $NR^5$ ;

n representing an integer with value 0, 1, 2 or 3;

$n'$  representing an integer with value 0 or 1;

wherein said  $R^2$  substituent, where possible, may optionally be substituted with at least one substituent selected from halo; hydroxy;  $C_{1-6}$ alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl,  $C_{1-4}$ alkyloxy,

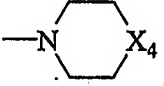
$C_{1-4}$ alkylcarbonyl,  $C_{1-4}$ alkyloxycarbonyl,  $C_{1-4}$ alkylcarbonyloxy,  $NR^6R^7$ ,

$-C(=O)-NR^6R^7$ ,  $-NR^5-C(=O)-NR^6R^7$ ,  $-S(=O)_{n1}-R^8$  or  $-NR^5-S(=O)_{n1}-R^8$ ;  $C_{2-6}$ alkenyl

or  $C_{2-6}$ alkynyl, each optionally substituted with at least one substituent selected from

- hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>6</sup>R<sup>7</sup>, -C(=O)-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>, -S(=O)<sub>n1</sub>-R<sup>8</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; polyhaloC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy optionally substituted with carboxyl; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylthio; polyhaloC<sub>1-6</sub>alkylthio;
- 5 C<sub>1-6</sub>alkyloxycarbonyl; C<sub>1-6</sub>alkylcarbonyloxy; C<sub>1-6</sub>alkylcarbonyl; polyhaloC<sub>1-6</sub>alkylcarbonyl; cyano; carboxyl; NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; -S-CN; -NR<sup>5</sup>-CN; aryloxy; arylthio; arylcarbonyl; arylC<sub>1-4</sub>alkyl; arylC<sub>1-4</sub>alkyloxy; a
- 10 5-or 6-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered monocyclic heterocycle optionally being substituted with at least one substituent selected from R<sup>9</sup>; or
- $$-(CH_2)_{n2}-X_2-(CH_2)_{n2}-N \begin{array}{c} \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \diagdown \quad \diagup \end{array} X_3$$
- with n<sub>2</sub> representing an integer with value 0, 1, 2, 3 or 4;
- with X<sub>2</sub> representing O, NR<sup>5</sup> or a direct bond;
- 15 with X<sub>3</sub> representing O or NR<sup>5</sup>;
- R<sup>3</sup> represents halo; hydroxy; C<sub>1-6</sub>alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>6</sup>R<sup>7</sup>, -C(=O)-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>, -S(=O)<sub>n1</sub>-R<sup>8</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl,
- 20 each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>6</sup>R<sup>7</sup>, -C(=O)-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>, -S(=O)<sub>n1</sub>-R<sup>8</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; polyhaloC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy optionally substituted with carboxyl; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylthio; polyhaloC<sub>1-6</sub>alkylthio;
- 25 C<sub>1-6</sub>alkyloxycarbonyl; C<sub>1-6</sub>alkylcarbonyloxy; C<sub>1-6</sub>alkylcarbonyl; polyhaloC<sub>1-6</sub>alkylcarbonyl; nitro; cyano; carboxyl; NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; -S-CN; -NR<sup>5</sup>-CN;
- R<sup>4</sup> represents hydrogen; halo; hydroxy; C<sub>1-4</sub>alkyl optionally substituted with at least one
- 30 substituent selected from hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>10</sup>R<sup>11</sup>, -C(=O)-NR<sup>10</sup>R<sup>11</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>10</sup>R<sup>11</sup>, -S(=O)<sub>n1</sub>-R<sup>12</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>12</sup>; C<sub>2-4</sub>alkenyl or C<sub>2-4</sub>alkynyl, each optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl,
- 35 C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>10</sup>R<sup>11</sup>, -C(=O)-NR<sup>10</sup>R<sup>11</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>10</sup>R<sup>11</sup>, -S(=O)<sub>n1</sub>-R<sup>12</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>12</sup>; polyhaloC<sub>1-3</sub>alkyl; C<sub>1-4</sub>alkyloxy optionally



- substituted with carboxyl; polyhaloC<sub>1-3</sub>alkyloxy; C<sub>1-4</sub>alkylthio;  
polyhaloC<sub>1-3</sub>alkylthio; C<sub>1-4</sub>alkyloxycarbonyl; C<sub>1-4</sub>alkylcarbonyloxy;  
C<sub>1-4</sub>alkylcarbonyl; polyhaloC<sub>1-4</sub>alkylcarbonyl; nitro; cyano; carboxyl; NR<sup>10</sup>R<sup>11</sup>;  
C(=O)NR<sup>10</sup>R<sup>11</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>10</sup>R<sup>11</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>12</sup>;  
5 -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>12</sup>; -S-CN; -NR<sup>5</sup>-CN;  
R<sup>5</sup> represents hydrogen or C<sub>1-4</sub>alkyl;  
R<sup>6</sup> and R<sup>7</sup> each independently represent hydrogen; cyano; C<sub>1-6</sub>alkylcarbonyl;  
C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkyl-NR<sup>5</sup>-C<sub>1-4</sub>alkyl; C<sub>1-6</sub>alkyl optionally substituted with  
hydroxy, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyloxy, NR<sup>6a</sup>R<sup>7a</sup>, C(=O)NR<sup>6a</sup>R<sup>7a</sup>,  
; with X<sub>4</sub> representing O or NR<sup>5</sup>;  
10 R<sup>6a</sup> and R<sup>7a</sup> each independently represent hydrogen; C<sub>1-4</sub>alkyl; C<sub>1-4</sub>alkylcarbonyl; a 5-  
or 6-membered monocyclic heterocycle containing at least one heteroatom selected  
from O, S or N;  
R<sup>8</sup> represents C<sub>1-4</sub>alkyl, polyhaloC<sub>1-4</sub>alkyl or NR<sup>6</sup>R<sup>7</sup>;  
15 R<sup>9</sup> represents halo; hydroxy; C<sub>1-6</sub>alkyl optionally substituted with at least one  
substituent selected from hydroxy, cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl,  
C<sub>1-4</sub>alkyloxycarbonyl, C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>6</sup>R<sup>7</sup>, -C(=O)-NR<sup>6</sup>R<sup>7</sup>,  
-NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>, -S(=O)<sub>n1</sub>-R<sup>8</sup> or -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; C<sub>2-6</sub>alkenyl or C<sub>2-6</sub>alkynyl,  
each optionally substituted with at least one substituent selected from hydroxy,  
20 cyano, carboxyl, C<sub>1-4</sub>alkyloxy, C<sub>1-4</sub>alkylcarbonyl, C<sub>1-4</sub>alkyloxycarbonyl,  
C<sub>1-4</sub>alkylcarbonyloxy, NR<sup>6</sup>R<sup>7</sup>, -C(=O)-NR<sup>6</sup>R<sup>7</sup>, -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>, -S(=O)<sub>n1</sub>-R<sup>8</sup> or  
-NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; polyhaloC<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy optionally substituted with  
carboxyl; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylthio; polyhaloC<sub>1-6</sub>alkylthio;  
C<sub>1-6</sub>alkyloxycarbonyl; C<sub>1-6</sub>alkylcarbonyloxy; C<sub>1-6</sub>alkylcarbonyl; cyano; carboxyl;  
25 NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>;  
-NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; -S-CN; -NR<sup>5</sup>-CN;  
R<sup>10</sup> and R<sup>11</sup> each independently represent hydrogen; C<sub>1-6</sub>alkyl; cyano;  
C<sub>1-6</sub>alkylcarbonyl; C<sub>1-4</sub>alkyloxyC<sub>1-4</sub>alkyl or C<sub>1-4</sub>alkyl-NR<sup>5</sup>-C<sub>1-4</sub>alkyl;  
R<sup>12</sup> represents C<sub>1-4</sub>alkyl or NR<sup>10</sup>R<sup>11</sup>;  
30 n1 represents an integer with value 1 or 2;  
aryl represents phenyl or phenyl substituted with at least one substituent selected from  
halo, C<sub>1-6</sub>alkyl, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyloxy, cyano, nitro, polyhaloC<sub>1-6</sub>alkyl and  
polyhaloC<sub>1-6</sub>alkyloxy.
- 35 2. A compound as claimed in claim 1 wherein ring A represents phenyl or pyridyl; R<sup>1</sup>  
represents hydrogen; X represents a direct bond or C<sub>1-4</sub>alkyl; R<sup>2</sup> represents phenyl

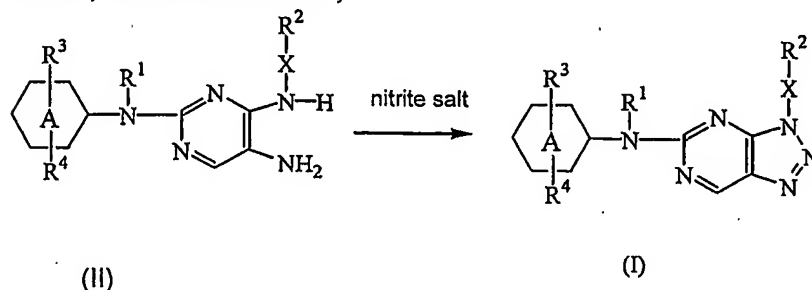
wherein said phenyl may optionally be substituted with at least one substituent selected from halo; C<sub>1-6</sub>alkyl optionally substituted with at least one substituent selected from hydroxy; C<sub>1-6</sub>alkyloxy; cyano; C(=O)NR<sup>6</sup>R<sup>7</sup>; arylC<sub>1-4</sub>alkyloxy; a 5-or 6-membered heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered heterocycle optionally being substituted with at least one substituent selected from R<sup>9</sup>; R<sup>3</sup> represents halo; hydroxy; C<sub>1-6</sub>alkyl optionally substituted with at least one substituent selected from hydroxy, cyano, carboxyl; C<sub>2-6</sub>alkenyl optionally substituted with at least one substituent selected from carboxyl, C<sub>1-4</sub>alkyloxycarbonyl; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkyloxycarbonyl; C<sub>1-6</sub>alkylcarbonyl; cyano; carboxyl; NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; -S-CN; R<sup>4</sup> represents hydrogen; halo; C<sub>1-6</sub>alkyl; cyano.

3. A compound as claimed in claim 1 or 2 wherein ring A represents phenyl or pyridyl; R<sup>1</sup> represents hydrogen; X represents a direct bond; R<sup>2</sup> represents phenyl wherein said phenyl may optionally be substituted with at least one substituent selected from halo; C<sub>1-6</sub>alkyloxy; C(=O)NR<sup>6</sup>R<sup>7</sup>; a 5-or 6-membered heterocycle containing at least one heteroatom selected from O, S or N and said 5-or 6-membered heterocycle optionally being substituted with at least one substituent selected from R<sup>9</sup>; R<sup>3</sup> represents halo; hydroxy; C<sub>1-6</sub>alkyl optionally substituted with at least one substituent selected from hydroxy; C<sub>2-6</sub>alkenyl optionally substituted with at least one substituent selected from carboxyl, C<sub>1-4</sub>alkyloxycarbonyl; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylcarbonyl; cyano; carboxyl; C(=O)NR<sup>6</sup>R<sup>7</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; R<sup>4</sup> represents hydrogen; halo; C<sub>1-6</sub>alkyl; cyano.

4. A compound as claimed in any one of claims 1 to 3 wherein the compound is selected from  
[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-benzonitrile;  
[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-yl]-(3-methanesulfonyl-phenyl)-amine;  
N-{3-[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-phenyl}-methanesulfonamide;  
1-{3-[3-(3-fluoro-phenyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-ylamino]-phenyl}-ethanone; a N-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

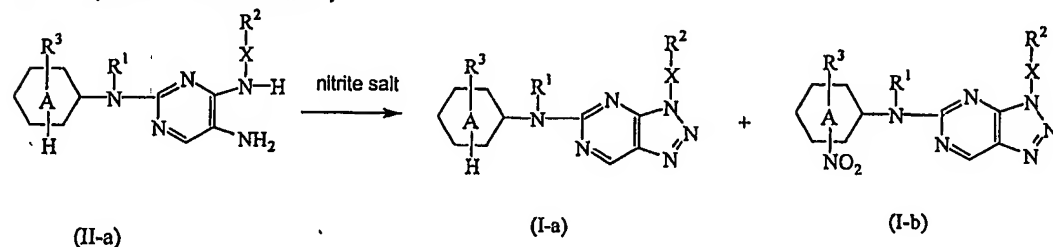
5. A compound as claimed in any one of claims 1 to 4 for use as a medicine.

6. The use of a compound as defined in any one of claims 1 to 4 for the manufacture of a medicament for the prevention or the treatment of diseases mediated through GSK3.
7. The use of a compound as defined in any one of claims 1 to 4 for the manufacture of a medicament for the prevention or the treatment of bipolar disorder (in particular manic depression), diabetes, Alzheimer's disease, leukopenia, FTDP-17 (Fronto-temporal dementia associated with Parkinson's disease), cortico-basal degeneration, progressive supranuclear palsy, multiple system atrophy, Pick's disease, Niemann Pick's disease type C, Dementia Pugilistica, dementia with tangles only, dementia with tangles and calcification, Down syndrome, myotonic dystrophy, Parkinsonism-dementia complex of Guam, aids related dementia, Postencephalic Parkinsonism, prion diseases with tangles, subacute sclerosing panencephalitis, frontal lobe degeneration (FLD), argyrophilic grains disease, subacute sclerotizing panencephalitis (SSPE) (late complication of viral infections in the central nervous system), inflammatory diseases, cancer, dermatological disorders, neuroprotection, schizophrenia, pain.
8. The use of a compound as claimed in claim 7 for the prevention or the treatment of Alzheimer's disease, diabetes, cancer, inflammatory diseases or bipolar disorder.
9. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4.
10. A process for preparing a pharmaceutical composition as claimed in claim 9 characterized in that a therapeutically effective amount of a compound as claimed in any one of claims 1 to 4 is intimately mixed with a pharmaceutically acceptable carrier.
11. A process for preparing a compound as claimed in claim 1, characterized by a) by cyclizing an intermediate of formula (II) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



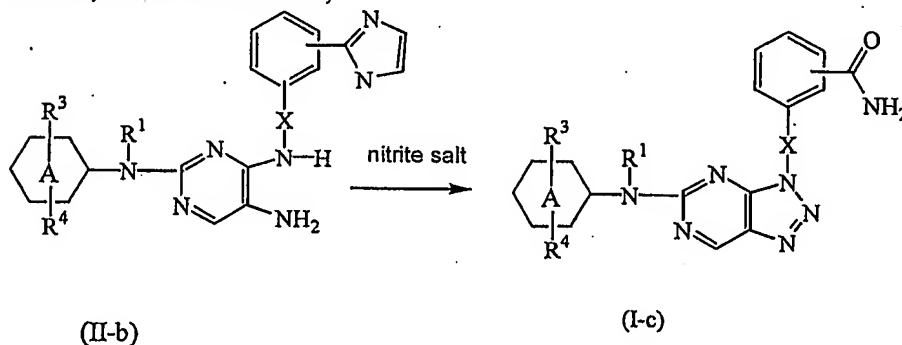
wherein ring A, R<sup>1</sup> to R<sup>4</sup> and X are as defined in claim 1;

b) cyclizing an intermediate of formula (II-a) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



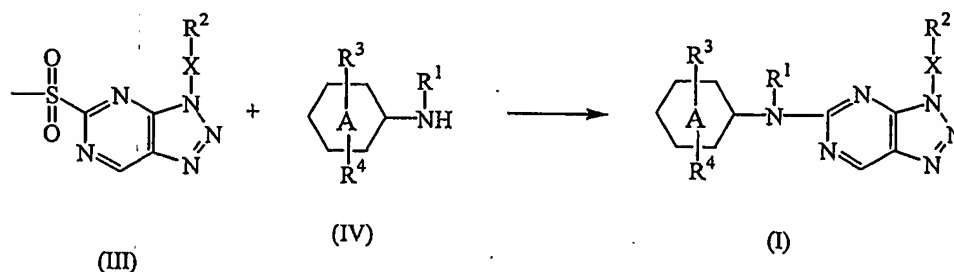
5 wherein ring A, R<sup>1</sup> to R<sup>3</sup> and X are as defined in claim 1;

c) cyclizing an intermediate of formula (II-b) in the presence of a nitrite salt, a suitable solvent, and a suitable acid,



wherein ring A, R<sup>1</sup>, R<sup>3</sup>, R<sup>4</sup> and X are as defined in claim 1;

10 d) reacting an intermediate of formula (III) with an intermediate of formula (IV) in the presence of a suitable solvent,



wherein ring A, R<sup>1</sup> to R<sup>4</sup> and X are as defined in claim 1;

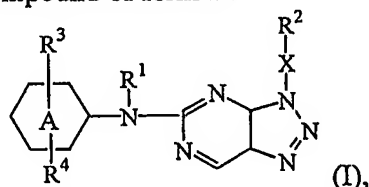
15 or, if desired, converting compounds of formula (I) into each other following art-known transformations, and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or into a therapeutically active non-toxic base addition salt by treatment with a base, or  
 20 conversely, converting the acid addition salt form into the free base by treatment with alkali, or converting the base addition salt into the free acid by treatment with acid; and,

if desired, preparing stereochemically isomeric forms, quaternary amines or *N*-oxide forms thereof.

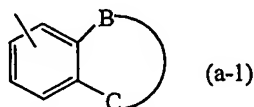
## ABSTRACT

5 TRIAZOLOPYRIMIDINE DERIVATIVES AS GLYCOGEN SYNTHASE KINASE 3  
INHIBITORS

This invention concerns a compound of formula



- 10 a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein ring A represents phenyl, pyridyl, pyrimidinyl, pyridazinyl or pyrazinyl; R<sup>1</sup> represents hydrogen; aryl; formyl; C<sub>1-6</sub>alkylcarbonyl; C<sub>1-6</sub>alkyl; C<sub>1-6</sub>alkyloxy; substituted C<sub>1-6</sub>alkyl; or optionally substituted C<sub>1-6</sub>alkyloxyC<sub>1-6</sub>alkylcarbonyl; X represents a direct bond; C<sub>1-4</sub>alkyl- or
- 15 -C<sub>1-2</sub>alkyl-X<sub>a</sub>-X<sub>b</sub>-; R<sup>2</sup> represents C<sub>3-7</sub>cycloalkyl; phenyl or a 4, 5, 6- or 7-membered monocyclic heterocycle containing at least one heteroatom selected from O, S or N; or a radical of formula



- wherein said R<sup>2</sup> substituent may optionally be substituted; R<sup>3</sup> represents halo; hydroxy;
- 20 optionally substituted C<sub>1-6</sub>alkyl; optionally substituted C<sub>2-6</sub>alkenyl; polyhaloC<sub>1-6</sub>alkyl; optionally substituted C<sub>1-6</sub>alkyloxy; polyhaloC<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylthio; polyhaloC<sub>1-6</sub>alkylthio; C<sub>1-6</sub>alkyloxy; C<sub>1-6</sub>alkylcarbonyloxy; C<sub>1-6</sub>alkylcarbonyl; polyhaloC<sub>1-6</sub>alkylcarbonyl; nitro; cyano; carboxyl; NR<sup>6</sup>R<sup>7</sup>; C(=O)NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>6</sup>R<sup>7</sup>; -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>8</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>8</sup>; -S-CN;
- 25 -NR<sup>5</sup>-CN; R<sup>4</sup> represents hydrogen; halo; hydroxy; optionally substituted C<sub>1-4</sub>alkyl; C<sub>2-4</sub>alkenyl or C<sub>2-4</sub>alkynyl, each optionally substituted; polyhaloC<sub>1-3</sub>alkyl; optionally substituted C<sub>1-4</sub>alkyloxy; polyhaloC<sub>1-3</sub>alkyloxy; C<sub>1-4</sub>alkylthio; polyhaloC<sub>1-3</sub>alkylthio; C<sub>1-4</sub>alkyloxy; C<sub>1-4</sub>alkylcarbonyloxy; C<sub>1-4</sub>alkylcarbonyl; polyhaloC<sub>1-4</sub>alkylcarbonyl; nitro; cyano; carboxyl; NR<sup>10</sup>R<sup>11</sup>; C(=O)NR<sup>10</sup>R<sup>11</sup>; -NR<sup>5</sup>-C(=O)-NR<sup>10</sup>R<sup>11</sup>;
- 30 -NR<sup>5</sup>-C(=O)-R<sup>5</sup>; -S(=O)<sub>n1</sub>-R<sup>12</sup>; -NR<sup>5</sup>-S(=O)<sub>n1</sub>-R<sup>12</sup>; -S-CN; -NR<sup>5</sup>-CN; ; their use, pharmaceutical compositions comprising them and processes for their preparation.